DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Division of Anti-Infective Products/Office of Antimicrobial Products

Briefing Document

Endpoints and Clinical Trial Issues in Community-Acquired Bacterial Pneumonia

Anti-Infective Drugs Advisory Committee

November 3, 2011

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I. Introduction

The purpose of this background document is to provide summary information on issues related to clinical trial designs and endpoints for community-acquired bacterial pneumonia (CABP) and describe outstanding issues where the FDA's Anti-Infective Drugs Advisory Committee (AIDAC) can provide additional input. There have been several public discussions of the design of clinical trials and efficacy endpoints for CABP. A workshop co-sponsored by the FDA and the Infectious Diseases Society of America (IDSA) in January 2008 and several meetings of the AIDAC have discussed issues related to CABP. A draft FDA guidance document on developing drugs for treatment of CABP was published for public comment in March 2009 to which numerous comments and concerns were expressed.

Based on the comments received and previous discussions at AIDAC meetings, as well as ongoing discussions, it is apparent that there are still unresolved issues regarding the clinical trial design and the practicalities of conducting informative noninferiority trials in CABP. The goal of this meeting is to discuss these unresolved issues in order to get advice on how they should be addressed in designing clinical trials for CABP. Development of new antibacterial drugs for treatment of patients with community acquired bacterial pneumonia, both intravenous and oral agents is essential in order to meet current and future public health needs.

The sections of this background document are organized by the previous AIDAC meeting summaries and current FDA approaches to CABP clinical trial designs and endpoints. The questions posed at this meeting of the AIDAC will provide more focused discussions on these unresolved issues. We seek the advice of the AIDAC on three specific areas:

1. Elements of clinical trial designs for CABP including primary and secondary efficacy endpoints, analysis populations of intent-to-treat (ITT) and microbiological intent-to-treat (micro-ITT), and non-inferiority margins

2. Approaches to enroll patients in clinical trials of CABP while avoiding the use of prior antibacterial drug therapy.

3. Advice on approaches to clinical trials of oral drugs for CABP

II. Summary of AIDAC Meetings and Events Pertaining to CABP

A. The April 1 & 2, 2008 AIDAC Meeting

The first of the AIDAC meetings pertaining to CABP occurred on April 1 & 2, 2008. Following a January 2008 workshop co-sponsored by the FDA and the IDSA on community-acquired pneumonia (CAP), the AIDAC met on April 1 & 2, 2008 to further

discuss clinical trial designs and endpoints. The following bullet points highlight the discussions during the meeting:

- The committee members offered unanimous support for the active-control trial design, because placebo-controlled trials would be unethical to conduct even in patients that have symptoms and signs of mild pneumonia.
- There was support for the noninferiority clinical trial design, but the AIDAC did not reach a consensus on what the primary endpoint should be when considering the M1, M2, and noninferiority margin.
- Some committee members provided comments that the difference in mortality observed from historical data from the 1940s could support an endpoint based on an appropriate clinical response outcome; other committee members provided comments that those data could support only mortality as an efficacy endpoint in a noninferiority trial design for CABP.
- There was agreement that bacterial confirmation of CAP (i.e., CABP) provides a stronger link to the historical data.
- Some committee members expressed concerns with the use of antibacterial drugs immediately prior to enrollment because this might confound the findings of efficacy in a noninferiority trial. It was also noted that empiric antibacterial therapy is administered promptly to persons with a presumptive diagnosis of CABP while under care in an emergency department or other urgent care settings; excluding such patients might compromise an ability to enroll patients in a clinical trial.

Based on the information assembled on CABP and the FDA-IDSA workshop and AIDAC discussions in 2008, the FDA posted a draft guidance document for CABP on March 20, 2009. The draft guidance outlined an endpoint of clinical response outcomes at a "test of cure" visit. This visit corresponds to the time when antibacterial drug therapy has been completed along with several days after completion of therapy to ensure overall clinical success, or to document clinical failure. Clinical success was defined as patients being alive with resolution of the disease-specific signs and symptoms that were present at enrollment. Clinical failure was defined as patients who died, or patients that lacked resolution of signs and symptoms or developed an infectious complication directly related to CABP (e.g., empyema). The draft guidance included a justification for a noninferiority margin that was based on the treatment difference in observed mortality rates from historical papers. The justification for a clinical response endpoint at a test of cure visit assumed that the effect size for a clinical response endpoint would be at least as large as the effect on mortality because a clinical response endpoint would include mortality and failure to attain a clinical response. In addition, there are probably some patients in present day trials who do not attain resolution of symptoms or developed infectious complications related to CABP and who would have died without appropriate modern patient care in a hospitalized setting. Such patients would be clinical failures. The guidance also recommended the exclusion of patients who received prior antibacterial drug therapy, and recommended that trials should evaluate the microbiologically-confirmed intent-to-treat (micro-ITT) population as the primary analysis population.

B. The December 9, 2009 AIDAC Meeting

As a result of numerous comments to the docket that criticized endpoints and clinical trial design issues in the draft guidance, a December 9, 2009 meeting of the AIDAC was convened to specifically discuss endpoints and clinical trial designs for CABP. Most of the criticisms of the clinical response endpoint arose from the limitations of the historical data and the lack of clear evidence for a treatment effect of an antibacterial drug for a clinical endpoint of resolution of signs and symptoms attributable to CABP at a "test of cure" time point. These comments noted that the historical data supported an all-cause mortality endpoint for the noninferiority trial design. As for other areas of clinical trial design, the comments in the docket provided concerns that the micro-ITT population as the prespecified analysis population would increase the sample size to a degree that clinical trials might not be practicable to conduct. Docket comments varied widely about the exclusion criterion of patients receiving prior antibacterial drug therapy; some comments lauded the exclusion because prior therapy would diminish the ability to detect a differential treatment effect, while other comments expressed concerns that the exclusion would limit an ability to enroll patients because of a policy or procedure for quality measures of prompt administration of antibacterial drug therapy for patients with suspected CABP.

The December 9 AIDAC discussion is highlighted in the bullet points provided below.

- The AIDAC provided nearly unanimous support (14 votes Yes, 2 votes No) for an all-cause mortality endpoint where the historical data support a treatment effect for that endpoint. Some committee members expressed concerns about the practicability of conducting a trial using the all-cause mortality endpoint because of low rates of mortality observed in recently-conducted trials, even when considering the odds ratio (instead of the rate difference) as the primary analysis parameter.
- The FDA presented historical data on favorable clinical responses earlier in the course of antibacterial drug therapy that appear to provide a large treatment difference between antibacterial drugs and no treatment. In response to the question, "Do the historical data presented support the use of clinical response as the primary endpoint in a CABP noninferiority trial?" 12 of the committee members voted "yes" and 4 voted "no". Comments from the committee included that the historical data appeared to be compelling [for a clinical response endpoint based earlier in the course of therapy] and that trials using a clinical response endpoint found daptomycin to be inferior to a comparison drug (see Appendix 2 "Discussion Topics on Endpoints and Clinical Trial Design for CABP" for a discussion about these endpoints and noninferiority margin justifications). Among the 4 committee members who voted "no", the main concern was the lack of information about how the clinical response endpoints were collected in the historical studies.

- Most of the committee members voted for the use of the micro-ITT population as the primary analysis population, but some committee members expressed concerns that trials may not be practicable to conduct because of the enhancement in the sample sizes to arrive at an appropriate sample size for an adequately powered micro-ITT analysis population.
- Most of the committee members voted in favor of excluding clinical trial participants that received prior antibacterial drug therapy. Concerns were also expressed that this exclusion criterion may make trials less practicable to conduct because patients receive prompt antibacterial drug therapy for presumed CABP balanced with the challenges in prompt enrollment of patients into a clinical trial.
- The committee felt that atypical pathogens could be included in the trial for CABP (Legionella for trials enrolling patients with "severe" CABP and Mycoplasma and Chlamydia in trials enrolling patients with "mild-to-moderate" CABP), with careful attention to the spectrum of antibacterial activity of the investigational drug and control drug as well as the concomitant use of antibacterial drug therapies in the trial.
- The committee favored the use of patient reported outcome measures (PROs) to be included as a primary efficacy measure in clinical trials of mild-moderate outpatient CABP designed for a finding of superiority over a control antibacterial drug.

C. Latest Submission of Comments to the Docket for the Draft Guidance

A working group of the Foundation for the National Institutes of Health (FNIH) was formed at the request of CDER/FDA to address the issue of endpoints for CABP (and also for Acute Bacterial Skin and Skin Structure Infections). Given the limitations of the available data, assembling a group of experts to assess the available data and make judgments to arrive at recommendations for practicable clinical trial endpoints and clinical trial designs for CABP considering these limitations and uncertainty. The comments from the FNIH working group were submitted to the docket on August 26, 2011. For the CABP endpoint, the working group evaluated retrospective data from several clinical trials in CABP. Symptoms of cough, amount of sputum production, chest pain, and shortness-of-breath were collected among several clinical trials. The review of data found that nearly all patients in trials presented with at least 2 of these 4 symptoms of CABP, and that 75% to 80% of patients experienced improvement in at least 2 (of the 4) symptoms of CABP, and no worsening of other symptoms and no new symptoms, at time points of approximately day 3 to day 5 of therapy for CABP. The interim endpoints as recommended by the FNIH working group included the improvement in at least 2 of the 4 symptoms identified (cough, amount of sputum production, chest pain, and shortness-of-breath). The working group also noted that other symptoms may be included and should be the subject of future research. See Appendix 1 for comments submitted to the docket in response to the draft CABP guidance document, including the FNIH's Biomarkers Consortium project team comments).

III. Current FDA Approach to Endpoints and Clinical Trial Designs for CABP for AIDAC Discussion

The Discussion Topics describes potential clinical trial design elements, primary and secondary efficacy endpoints, and analysis populations (ITT and micro-ITT) for CABP trials (see Appendix 2). The summary below provides an overview of the important areas where we seek information based on the AIDAC's discussion.

A. Clinical Endpoints for CABP Based on Symptom Improvement

As noted in a 2011 report from the Institute of Medicine of the National Academies (IOM), a Committee on Qualification of Biomarkers and Surrogate Endpoints was established when the Center for Food Safety and Applied Nutrition (CFSAN), in conjunction with the Center for Drug Evaluation and Research (CDER), approached the IOM for advice on the topic of biomarker and surrogate endpoint evaluation in chronic disease.[1] The document explicitly states that clinical endpoints should capture how patients feel, function, or survive and should be closely related to events that affect patients' lives.

As work is being done to fully characterize a new and clinically meaningful efficacy endpoint for CABP, we believe that an interim endpoint that is based upon improvement in at least 2 symptoms attributable to CABP should include, at a minimum, cough, sputum production, chest pain, and shortness-of-breath at an early time point (i.e., day 3 to day 5 after enrollment) can be utilized.

We encourage the performance of additional developmental work on an instrument to assess a symptom-response endpoint for CABP that also captures elements of improvement in clinical signs,[2] from the perspective of the patient (as patients experience the manifestations of these physiologic abnormalities); such an approach may best describe overall clinical improvement that was characterized by clinicians in the 1930s and 1940s.

In our work to assess treatment effects in CABP and in arriving at a recommended interim endpoint and areas for additional endpoint development in CABP we have also had to make judgments regarding the limitations of the available data and attendant uncertainty. In our review of the available historical information and retrospective analyses of clinical trial data we noted the following limitations:

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[1] For more information, the IOM report *Perspectives on Biomarker and Surrogate Endpoint Evaluation: Discussion Forum Summary* can be access at the National Academies Press web page at: http://www.nap.edu/catalog/13038.html

[2] For a description of improving clinical signs or clinical stability in patients with CABP, see Mandell LA, Wunderink RG, Anzueto A, et. al., 2007. Infectious Disease Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis; 44: S27-72.

- that symptoms were recorded by the clinical trial site clinicians, and not by the patients themselves
- the protocols did not provide standardized guidelines or instructions for how the clinicians were to ascertain from the patient whether the symptom was absent, mild, moderate, or severe
- the case report form contained boxes for the clinical trial clinician to check for each symptom as being "absent", "mild", "moderate", or "severe"
- an established treatment effect or historical evidence for sensitivity to drug effects (HESDE) was based on an overall clinical assessment; symptom-based improvements were included as part of the overall clinical assessment but were not described separately (cough, sputum production, chest pain, shortness of breath).
- Our review of the literature suggested a treatment difference based on the objective clinical assessments, which in the 1930s and 1940s included, in part, signs (e.g., body temperature, blood pressure, pulse, respiratory rate) as well as symptoms.

Despite these limitations, we have attempted to make reasonable judgments on clinical trial designs, endpoints, and analysis populations to provide recommendations on scientifically sound, ethical, and feasible clinical trial designs for CABP.

While work on a new symptom endpoint is being developed and an interim symptom-response endpoint is used as the primary efficacy endpoint, an essential secondary endpoint for evaluation should be improvement or stability in clinical signs at day 3 to day 5. Recording objective information on clinical signs could also help to characterize a new endpoint based on symptom improvement and its relationship to overall clinical improvement.

We also believe that is important to evaluate endpoints that reflect the clinical status of the patient at observation after completion of treatment (e.g., the "test of cure" visit). It is important to document that patients are maintaining a successful response to antibacterial drug treatment, or that patients have re-initiated antibacterial drug treatment during the period of observation after completion of antibacterial drug treatment. Objective outcome assessments at a "test of cure" visit should be regarded as important secondary outcome assessments.

We will ask the AIDAC to discuss the use of a symptom improvement outcome as the interim primary efficacy endpoint for trials of CABP, and whether the 4 symptoms of cough, sputum production, chest pain, and shortness of breath are sufficient for use. The AIDAC will be asked to comment on the role of improvement or stabilization of clinical signs in trials of CABP as secondary outcome assessments.

B. Approaches to Defining the Microbiological Intent-to-Treat (micro-ITT) Population

Previous AIDAC discussions have generally agreed that a micro-ITT population ensures a patient population with CABP for the noninferiority analysis. In recently conducted clinical trials, it appears that 25% to 30% of patients have bacterial pathogens detected on cultures of sputum. Therefore, a prespecified analysis population for clinical trials based on the micro-ITT population requires that 3 to 4 times as many patients as needed to obtain the 25-30% with a microbiological diagnosis for analyses based on the micro-ITT population. Attempts to enhance the identification of bacterial pathogens would have favorable implications for conducting clinical trials in CABP.

New diagnostic methods appeared to enhance the microbiological yield in one publication.[3] Johansson and colleagues report a rate of documented microbial etiology of 67%. This rate included both viral and bacterial pathogens. Table 2 in this publication lists the bacterial yield in the population with community-acquired pneumonia. Of 184 patients with clinical findings consistent with CAP, 55 had a bacterial etiology on blood culture, pleural fluid culture, or sputum culture (55/184 or 29.9%), which is a finding consistent with the proportion of patients with a bacterial etiology identified in current clinical trials of CABP. With urinary antigen testing for *S. pneumoniae* and *L. pneumophila* and polymerase chain reaction (PCR) for *S. pneumoniae* and *H influenzae* from sputum, it appears from Table 2 that additional patients were identified as having a bacterial etiology for CAP despite having negative sputum cultures. The authors described an overall bacterial yield that exceeded 50% of patients with CAP, but the authors included cultures or PCR results of nasal secretions. We do not believe that there is presently sufficient information to support the use of data from nasal secretions to define the micro-ITT population for CABP. Nevertheless, this paper demonstrates that it appears possible to enhance the proportion of patients included in a micro-ITT analysis population with the use of nonculture test methods from appropriate specimens.

Conventional sputum culture for all patients in a CABP trial is needed for the evaluation of microbiological data including the characterization of in vitro susceptibility testing. However, the use of nonculture tests can be used for the purpose of defining the micro-ITT efficacy analysis population, when conventional sputum cultures have no growth in patients with a high suspicion for CABP. A test that is cleared by FDA/CDRH represents a straightforward approach to consider (e.g., urinary antigen testing for *S. pneumoniae*). Tests that have not been cleared by FDA/CDRH may still be used for the purpose of defining the micro-ITT efficacy analysis population, but data on the performance characteristics should be submitted to FDA for review. Based on our review it would be determined whether or not the test is an acceptable means to identify patients for the micro-ITT efficacy analysis. If a test is used in a trial for assistance in clinical management decisions for patients (i.e., not just for identifying patients for an analysis population), an Investigational Device Exemption (IDE) may be necessary and advice from FDA should be sought before the trial is initiated.

[3] Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis 2010;50:202-209.

As a practical concern it may be desirable to include cough productive of sputum as a required entry criterion, which might enhance the possibility of identifying a bacterial pathogen on sputum culture. In addition, sputum induction by experienced respiratory therapists at the clinical trial sites might enhance the possibility of identifying the bacterial etiology for CABP by standard sputum culture.

We will ask the AIDAC to discuss methods of enhancing the micro-ITT population, including the use of nonculture methods from appropriate specimens, such as PCR testing of sputum or urinary antigen testing.

C. Possible Approaches to Clinical Trial Designs, Endpoints, and Analysis Populations to Arrive at Scientifically Sound, Ethical, and Feasible CABP Clinical Trials

The AIDAC discussions highlighted the importance of the micro-ITT population as the primary analysis population. The identification of a bacterial pathogen ensures that the analysis population has CABP. Thus, the analysis population will exclude patients that have self-limiting viral respiratory infections or other nonbacterial pulmonary processes and also patients with a bacterial etiology that remains undetected; including such patients may bias the results towards a finding of noninferiority.

However, AIDAC discussions, docket comments, workshop discussions, and publications have pointed out that only 25% to 30% of patients have a documented bacterial pathogen by conventional sputum culture methods in clinical trials for CABP. The enhancement of the micro-ITT population based on nonculture methods appears encouraging, but the additional patients for which a diagnosis is made using currently available nonculture methods may not substantially increase the proportion of patients for whom a microbiologic diagnosis is identified.

In trials of CABP, the clinical and radiographic criteria should enhance the population for patients more likely to have a bacterial etiology for CABP. In addition, when there is a more extensive search for an underlying microbiological diagnosis some patients with CABP and negative sputum cultures had bacterial pathogens identified through other means, such as a transtracheal aspiration procedure.[4]

Recognizing the issues around feasibility of clinical trials in CABP, the limitations of currently available diagnostics, a proposal for discussion at AIDAC is one in which two adequate and well-controlled noninferiority trials are conducted with identical protocols. Each trial should have sufficient power to demonstrate noninferiority on the basis of the intent-to-treat (ITT) population, where the enrollment criteria for patients should

[4] Østergaard L, Andersen PL. Etiology of community-acquired pneumonia: evaluation by transtracheal aspiration, blood culture, or serology. Chest 1993;104:1400-1407; and Ruiz-González A, Falguera M, Nogués A, Rubio-Caballero M. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. Am J Med. 1999 Apr;106(4):385-90.

minimize a concern that patients may have self-limiting viral respiratory pathogens or nonbacterial pulmonary processes (e.g., congestive heart failure, pulmonary edema). When the ITT population has demonstrated noninferiority in each of the two trials, the subgroup of patients from both trials who fall within the micro-ITT may be pooled for an evaluation of noninferiority. The following example has more detail for sample size estimations using differing power calculations and noninferiority margins for this approach.

Using an interim endpoint of improvement in symptoms at day 3 to day 5, we assumed the rate of success is 80 percent. We also assumed a 2-sided type 1 error (α) of 0.05 and type 2 error (β) of 0.10 (power 0.90) for each of the ITT analyses and overall the type 2 error (β) of 0.20 (power 0.80)[5], and a noninferiority margin of 10 percent for the ITT analyses and a noninferiority margin of 15 percent for the micro-ITT analysis. It may be reasonable to expect that 27% of patients will have microbiological diagnosis of a bacterial etiology for CABP. In this case, a total of approximately 344 patients per arm should be enrolled in each trial using a 1:1 randomization to investigational drug or active-control drug. The total number of patients for both trials would be approximately 1376 patients (344 patients per arm in each of two trials). Appendix 3 contains several tables of sample size estimates based on different assumptions regarding overall power and noninferiority margins.

In summary, noninferiority would be demonstrated based on a co-primary hypothesis (H1 and H2):

> H1: demonstration of noninferiority (using 10% margin) independently for both trials in the ITT populations
>
> H2: demonstration of noninferiority (using 15% margin) for the weighted pooling of the micro-ITT population as a single analysis.

The AIDAC will be asked to discuss the approach to using a pooled micro-ITT population from 2 noninferiority trials and the implications for selecting a noninferiority margin of 15% for the pooled micro-ITT analysis population for a primary endpoint based on symptom resolution.

D. Use of Antibacterial Drugs Immediately Prior to Trial Enrollment

The topic of the prior use of antibacterial drugs has been addressed at several AIDAC meetings. The committee has been nearly unanimous in its recommendations for the exclusion criterion of the administration of antibacterial drugs immediately prior to enrollment. The committee has also provided some comments that this requirement may make clinical trials difficult to conduct because of the policies and procedures established at healthcare institutions to initiate antibacterial drug therapy promptly, usually within a

[5] In the sample size calculation the power is estimated at 0.904 for each of the two ITT analyses and 0.951 for the pooled micro-ITT analysis; for all analyses the power is estimated to be 0.80.

4-hour time frame. In addition, FDA recommends enrichment of a clinical trial population of patients who have greater severity of illness. Patients who are severely ill and are undergoing care to stabilize their delirium and oxygenation status acutely may not make ideal patients to approach for prompt enrollment into a clinical trial.

The analysis by Pertel, et al,[6] is cited to support the reason for why prior antibacterial drugs should not be allowed in clinical trials of CABP. This was a subgroup analysis from patients with acute bacterial pneumonia and randomized to receive either ceftriaxone or daptomycin in two nearly identical clinical trials. As noted in the publication, "When the results from the first study revealed that daptomycin did not meet predetermined criteria for noninferiority, enrollment in the second ongoing study was stopped." In an analysis of patients pooled from both trials, the subgroup of patients randomized to receive daptomycin who received previous antibacterial drug therapy of greater than 24 hours duration had similar treatment responses to patients that received ceftriaxone. Clinical cure rates among patients randomized to received daptomycin were 90.7% among patients with prior effective antibacterial drug therapy and 75.4% among patients that did not receive prior therapy; cure rates were approximately 88% for patients randomized to receive ceftriaxone regardless of whether or not they received prior effective antibacterial drug therapy (clinically evaluable populations). FDA has done its own subgroup analysis from these data, and found that patients who were randomized to receive daptomycin and received *short-acting* antibacterial drugs (i.e., less than 24 hours of prior antibacterial drugs) also appeared to have more favorable responses than patients who were randomized to receive daptomycin and did not receive any prior antibacterial drugs.

The AIDAC will be asked to discuss the issues of prompt enrollment procedures for clinical trials of CABP. For example, enrolling patients at presentation to an emergency room and using prompt informed consent procedures to ensure a patient population sufficiently ill from CABP that will receive either investigational drug or control drug throughout the entire course of therapy for CABP.

IV. Outlines of Possible CABP Development Pathways and Phase 3 Trial Designs

1. Two noninferiority trials:

- Primary endpoint at Day 3-5, i.e. symptom improvement/no worsening of dyspnea, cough, sputum production and chest pain (± exercise tolerance, feverishness, chill/rigors)
- Assumes 80% success rate in the control group
- ITT analyses in each trial and a pooled micro-ITT analysis across trials
- NI margin of 10% for ITT analysis in each trial

[6] Pertel PE, Bernado P, Fogerty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 2008; 46: 1142-1151.

- NI margin of 15% for the pooled micro-ITT analysis
- Approximately N=1376 total subjects (or 688 per trial, 344 subjects per arm)
- Key secondary endpoint of stabilization/normalization of vital signs at Day 3-5
- Key secondary endpoint of clinical response at EOT
- Assumes 27% of subjects are microbiologically evaluable
- 80% power for meeting all primary analysis requirements

2. Two noninferiority trials:

- Coprimary endpoint of signs and symptoms at Day 3-5, i.e. stabilization/normalization of vital signs and improvement/no worsening of dyspnea, cough, sputum production and chest pain
- Assumes 80% success rate on symptoms and 70% success rate on signs in the control group
- Coprimary ITT analyses in each trial and a pooled micro-ITT analysis across trials
- NI margin of 10% for ITT analysis in each trial
- NI margin of 15% for the pooled micro-ITT analysis
- Approximately N=1960 total subjects (or 980 per trial, 490 per arm)
- Key secondary endpoint of clinical response at EOT
- Assumes 27% of subjects are microbiologically evaluable
- 80% power for meeting all primary analysis requirements

3. One noninferiority trial:

- Primary endpoint at Day 3-5, i.e. improvement no worsening of dyspnea, cough, sputum production and chest pain (± exercise tolerance, feverishness, chill/rigors)
- The micro-ITT is the primary analysis population
- Assumes 80% success rate in the control group
- N=1862 total subjects (931 subjects per arm) if margin is 10%
  N=1192 total subjects (596 subjects per arm) if margin is 12.5%
  N=828 total subjects (414 subjects per arm) if margin is 15%
- Assumes 27% of subjects are microbiologically evaluable
- 80% power for meeting primary analysis
- Supportive info could include:
  - A successful HABP trial if drug is broad spectrum or has activity against Gram-positive organisms
  - A successful ABSSSI trial if drug has activity against Gram-positive organisms

V. Topics for Discussion

1. Please discuss the merits and limitations of an endpoint based upon improvement in at least 2 of the 4 symptoms of cough, amount of sputum production, chest pain, and difficulty breathing (and no worsening or no new symptoms) at day 3 to day 5 as the primary endpoint for CABP trials. In your discussion, please comment on a noninferiority justification based on historical data showing a treatment effect on clinical responses noted at day 3 to day 5 of therapy.

2. Please discuss the merits and limitations of each of the proposed development pathways and trial designs. In your discussion, please comment on the use of improvement or stabilization of clinical signs of pneumonia as a co-primary endpoint versus its use as a secondary endpoint.

3. Please discuss any other possible trial designs, issues with receipt of prior antibacterial therapy, proposed endpoints, methods to enrich the micro-ITT population, and mechanisms to overcome barriers to trial conduct and any advice on performing clinical trials of oral antibacterial drugs (i.e., when an intravenous formulation is not available).

APPENDIX 1: Comments Submitted to the Docket in Response to the CABP Guidance

Wyeth Pharmaceuticals Inc.
P.O. Box 8299
Philadelphia, PA 19101-8299

Wyeth

June 17, 2009

0222 9 JUN 18 P12:26

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2009-D-0136, March 20, 2009 (74 FR, 11963 - 11964)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the Draft Guidance for Industry entitled, "Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment."

Wyeth is one of the largest research based pharmaceutical and healthcare products companies and is a leading developer, manufacturer, and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications. Wyeth appreciates the opportunity to comment on the above-mentioned Federal Register notice and supports the Agency in its efforts to provide guidance regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of community-acquired bacterial pneumonia (CABP). In support of this guidance and its intent, we are providing the following comments for your consideration.

A. Guidance for Atypical Bacterial Pathogens

While the guidance is entitled, "Community-Acquired Bacterial Pneumonia", the guidance specifically excludes community-acquired pneumonia resulting from atypical bacteria (e.g., Lines 43-33). However, the current Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) Consensus Guidelines on the Management of Community-Acquired Pneumonia notes (p. S44) that the atypical pathogens are among the most common etiologies of community-acquired pneumonia. The IDSA/ATS guidelines also state (p. S49), "The atypical pathogens responsible for severe CAP may vary over time but account collectively for ≥20% of severe pneumonia episodes."

Additionally, we are concerned that recommendations on conducting studies in an outpatient setting for atypical pathogens (e.g., *M. pneumoniae, C. pneumoniae*) known to cause community acquired pneumonia and commonly treated in an outpatient setting, are not available.

FDA-2009-D-0136

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Wyeth

We therefore recommend that the Agency hold a public workshop to seek recommendations from infectious disease experts on the design of clinical trials for drugs to support an indication for the treatment of community-acquired atypical bacterial pneumonia, including recommendations on the conduct of such studies in an outpatient setting. In addition, to support the development of antibacterial drugs to treat atypical pathogens, we further recommend that the Agency utilize the recommendations from the proposed public workshop to develop a future guidance for industry specific to this indication.

B. Clarification of MITT

The draft guidance states (Line 422-423), "...and the modified intent-to-treat (MITT) populations." We believe the intent of this statement was to state "and the microbiological intent-to-treat populations", as noted in Lines 609-610.

To avoid potential confusion with the "modified intent-to-treat population" and ensure clarity, we recommend that the statement be revised to "microbiological."

C. Validated PRO Instruments

We acknowledge that, to date, a validated Patient Reported Outcome (PRO) instrument has not been recognized by the FDA in CABP (Line 488). However, we believe that making such an explicit statement in the guidance may unnecessarily cause a Sponsor to initiate the development of a PRO when subsequent to the issuance of the guidance; one may have been validated and recognized by FDA.

We recommend that the guidance be revised to delete (Line 488) "Because no PRO instrument has been recognized by the FDA for this indication,...."

We are submitting the above comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned proposed draft guidance and trusts that the Agency will take these comments into consideration.

Sincerely,

Roy J. Baranello, Jr.
Assistant Vice President
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Global Research & Development

June 9, 2009

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket FDA-2009-D-0136 Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment[1]

Dear Sir or Madam,

Pfizer, a global research-based pharmaceutical company, submits the following comments in response to the *Federal Register* notice of March 20, 2009 (74 Fed. Reg.11963).

We would like to thank the FDA for the opportunity to comment on the draft CABP (Community-Acquired Bacterial Pneumonia) guideline. Our comments are based on our antibacterial development experiences and address clinical development and regulatory issues that may be encountered by sponsors seeking approval for therapies to treat CABP. Overall, we would like to highlight the following key points:

I. INTRODUCTION

The guidance divides study criteria based on formulation (IV vs. Oral) which seems artificial and not reflective of real world scenarios which frequently includes switching from an IV to oral therapy when clinically indicated. Sponsors should have the option of IV to oral switching in all pivotal trials providing appropriate PK/PD has been demonstrated between formulations.

The guidance recommends patients in IV antibacterial trials may need to be enrolled in an ER setting to preclude prior use of antibiotics. Enrolling patients only in an ER setting for IV antibacterials may result in unnecessary increased trial costs and may not be operationally feasible. We request that consideration be given allowing a single dose of anti-bacterial therapy prior to enrollment in the study.

[1] 74 FR 53 March 20, 2009, Federal Register Docket No. FDA-2009-D-0136.

Although this guidance is not meant to cover all potential pathogens, we think it is reasonable to include atypical bacterial pathogens (e.g. *L. pneumophilia, M. pneumoniae, and C. pneumoniae)*, given that these pathogens are frequent causes of CABP, and that improved diagnostics are now available.

III. DEVELOPMENT PROGRAM

A. General Considerations

FDA requirement for IV only trials – The guideline indicates if an IV formulation is available, an IV only study should be conducted to support a CABP claim. It may not be operationally feasible to conduct studies with IV only formulations where clinical practice dictates transitioning patients to an oral formulation when they have demonstrated clinical improvement. Investigators in the field may not agree to participate using an IV only study design. This approach is also anticipated to result in unnecessary increased costs for study conduct due to extended time in hospital which may not be clinically required. We request that the guidance is changed to reflect current medical practice allowing IV to oral switching and not mandating IV only studies.

Corroborative Clinical Evidence – The draft guideline offers the possibility that clinical studies in other respiratory infections may lend support to a CABP indication. We request additional FDA discussion regarding this point. This would include guidance on acceptability of using CABP data from pediatric population studies to provide corroborative evidence of safety and efficacy to support regulatory approval in adults. Also, we request additional discussion regarding circumstances where clinical trials in other respiratory tract infections could provide corroborative evidence in CABP.

Pharmacokinetics/Pharmacodynamics – Wording in the current guideline discusses the potential validity of tissue drug concentrations for PD assessments. We suggest more specific wording such as: "Information regarding drug exposure and pharmacokinetics in the affected compartment of the species being studied is important in interpreting the pharmacodynamic response. Where possible, the methodology employed should provide the opportunity to translate the measurement to clinical use (e.g. lung lavage fluid)." We propose additional statements on possible impact of species-specific protein binding e.g. "Information on plasma protein binding differences between animals and man may be important in interpreting and extrapolating pharmacodynamic data from animal species".

Pathogens – The current version of the guideline states that a trial in which most patients have documented bacterial pathogens (e.g., *S. pneumoniae*, *H. influenzae*, *S. aureus*, or *M. catarrhalis*) generally will provide the strongest evidence of efficacy. We request clarification in the guidance document that in order to garner a claim for CABP, not all of the listed pathogens would need to be studied e.g. *S. aureus* infections are relatively infrequent in CABP infections. In addition, as stated above, it is reasonable to include relevant atypical bacteria, such as *L. pneumophilia, M. pneumoniae, and C. pneumoniae* in the list of possible pathogens.

B. Specific Efficacy Trial Considerations- Efficacy Endpoints

PROs – Patient Reported Outcomes can be an important part of the assessment of effectiveness of therapies being developed for treatment of CABP. We believe a significant body of evidence supporting use of PRO instruments for pneumonia has been reported in the literature. This literature includes:

a. Lamping DL, Schroter S, Marquis P, Marrel A, Duprat-Lomon I, Sagnier PP, *"The Community-Acquired Pneumonia Symptom Questionnaire - A New, Patient-Based Outcome Measure To Evaluate Symptoms in Patients With Community-Acquired Pneumonia"*, Chest. *2002 Sep;122(3):920-9, and*

b. *David N. Gilbert, Clinical End Points of Therapy for Patients with Mild Community-Acquired Pneumonia", Department of Infectious Diseases, Providence Portland Medical Center, and Department of Medicine, Oregon Health and Sciences University, Portland, Oregon "Clinical End Points of Therapy for Patients with Mild Community-Acquired Pneumonia", Infectious Diseases 2008; 47 (Supp 3) :S140–44*

We would like the FDA to provide additional discussion on the validation and potential use of these instruments as well as others reported in the literature in the revised guideline. An FDA sponsored workshop on PROs for CABP would also be useful for sponsors to design clinical trials to support applications for marketing approval.

Choice of Comparators – It would be useful for the guidance to discuss FDA's willingness to consider the use of non-FDA approved comparators, particularly for ex-U.S. studies where the U.S. comparator is not available. This is especially relevant for sponsors wishing to conduct clinical trials on a global basis.

Concomitant Medications – The guidance states concomitant antibacterial therapy for other infections should not be allowed during the trial until after TOC visit. This could imply coverage for organisms not included in the spectrum of the study drug is not allowed. This could also pose an issue with achieving adequate levels of participation in the study. The use of a single dose of a short-acting antibacterial in addition to the study drug merits further consideration. We request that this is discussed in next version of guidance.

Trial Visits and Timing of Assessments – Please provide guidance on percent required for microbiologic sampling. Also, we request the next version of the guideline clarifies TOC timing for two different studies with varying lengths of therapies. Should they be the same or are there circumstances where they could vary due to local treatment practices? We propose alternative text for this section "Test-of-cure visit should occur at a fixed point in time relative to randomization (5-10 days after completion of the longer course of therapy)."

C. Other Considerations

Supporting Antimicrobial Resistant Claims – We would like FDA to provide additional guidance regarding the development of antibacterial therapies for treatment of CABP infections due to drug resistant pathogens. This request is especially relevant as the current draft says once issued, the new guideline will supersede the previous *"Clinical Evaluation of Anti-Infective Drugs and Clinical Development and Labeling of Anti-Infective Drug products"*. This superseded guideline discusses FDA requirements to demonstrate efficacy versus drug resistant pathogens to support resistant pathogen labeling claims. The old guideline states, "at least 10% of the evaluable cases meeting both clinical and microbiological evaluability criteria or 10 total cases, whichever is higher." We request that the revised guidance document discuss current FDA policy regarding required numerical numbers of resistant pathogens to be studied in CABP clinical trials, often referred to as the "*rule-of-ten*", to support including the resistant pathogen in product labeling. We also request additional discussion regarding conditions and circumstances in which pooling of resistant pathogens across related indications, studies, or populations (i.e. pediatric) would be appropriate. For example, what conditions could support pooling of RTI (Respiratory Tract Infections) across different sites/studies (assuming a sound PK/PD rationale) to achieve sufficient clinical and microbiological experience to support including resistant pathogen claims in product labeling per FDA "*rule-of-ten*".

Pneumococcal Vaccines – Pneumococcal vaccination is increasingly used in U.S. populations, both in the young and in the elderly. Given the likelihood of more frequent use of next-generation pneumococcal vaccines in adults (especially in the elderly), we recommend that pneumococcal vaccination status be tracked among future enrollees in CABP trials.

Special Populations – We are requesting additional FDA guidance on the clinical development of antibacterials in pediatric CABP. Specifically, circumstances where pediatric data could be bridged to a robust adult program to demonstrate acceptable benefit-risk in this special population. Also, under what circumstances demonstrated efficacy due to MDR pathogens could be extrapolated between the adult and pediatric populations to support a claim e.g. pathogen pooling to support labeling.

Pneumococcal Bacteremia – It has been reported that approximately 1.1 million patients are hospitalized with pneumonia each year in the United States. The reported frequency of bacteremia in these patients varied from as low as 4% to as high as 14 to 18% in severely ill patients *(American Journal of Respiratory and Critical Care Medicine, Vol 169, 2004)*. Sponsors will want develop therapies for this special population. We would therefore like FDA to provide additional guidance regarding clinical development of therapies to treat CABP infections with concurrent *pneumococcal* bacteremia. A discussion of current FDA policy regarding study designs and regulatory criteria to support a bacteremia claim due to CABP is warranted.

We would like to thank the FDA for the opportunity to comment on the draft CABP (Community-Acquired Bacterial Pneumonia) guideline.

Please do not hesitate to contact Peter DiRoma at peter.j.diroma@pfizer.com if there are any questions or if clarification or information is desired. I can also be reached at (860) 732-2414.

Sincerely,

Peter DiRoma
Senior Director
Worldwide Regulatory Strategy

Alan Goldhammer, PhD
Vice President,
Scientific & Regulatory Affairs

PhRMA

June 17, 2009

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket Number FDA-2009-D-0136; Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment; 74 Federal Register 11963; March 20, 2009

Dear Sir or Madam:

In response to the March 20, 2009 issuance of the "Draft Guidance for Industry – Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment," the Pharmaceutical Research and Manufacturers of America (PhRMA) is hereby submitting public comments to Docket Number FDA-2009-D-0136. PhRMA is a voluntary, non-profit trade organization representing the firms that discover, develop and produce prescription drugs and biologic products. PhRMA-member firms produce the large majority of new prescription medicines approved for marketing in the United States.

PhRMA supports FDA's practice of developing draft guidances and agrees that a well developed guidance for the development of drugs to treat Community-Acquired Bacterial Pneumonia will be constructive and generally helpful by making the requirements for drug development programs more transparent for industry.

The new Draft guideline attempts to assure enrollment of patients with both bacteriologic confirmed diagnosis as well as meaningful severity so that analysis of treatment effect is on patients with credible disease.

A PhRMA Task Group has reviewed the Draft Guidance and would like to take this opportunity to provide the following comments as the Draft Guidance is finalized:

1. Requirements for Specific Distributions of subjects by PORT (Fine, PSI) Class

The use of PORT scores to guide enrollment is explained (lines 1011-1028) as a way to ensure an adequate level of risk in the enrolled population. However, the strongest demonstration of antibiotic effect from the available historical data is found in the reduction of mortality for subjects aged ≥ 50 years (Fleming TR, Powers JH. Clin Infect Dis 2008;47:S108-S120, Dowling and Lepper, Am J Med Sci, 1951;222:396-402). The contribution of age as the primary driver for

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risk was also observed in Katherine Laessig's analysis of the most recent data (Anti-infective Drug Advisory Committee meeting on June 2, 2009). As stated by the Draft Guidance in its discussion of risk factors associated with severity (lines 1009-1028):

> *"Age is a strong predictor of mortality in CAP, and from the historical studies … there was a larger treatment effect in patients older than 50 years of age. As noted in Table A3, the point estimate for treatment effect approximately doubles in the patient population older than 50 years of age compared to the population younger than 50 years of age."*

Enrolling a higher proportion of patients aged $\geq$ 50 years with a positive bacterial culture will create a convincing link to the historical evidence for efficacy. However, we disagree with the use of PORT classification to achieve this goal. PORT was not developed as a severity score. This problem is made clear in the recent American Thoracic Society (ATS) guidelines (Mandell LA et al. Clin Infect Dis 2007;44 Suppl 2:S27-72):

> *For example, a previously healthy 25-year-old patient with severe hypotension and tachycardia and no additional pertinent prognostic factors would be placed in risk class II, whereas a 70-year-old man with a history of localized prostate cancer diagnosed 10 months earlier and no other problems would be placed in risk class IV.*

Finally, the use of accurate PORT scores in clinical trials is dependent on the collection of many patient disease characteristics at the time of randomization. This includes various laboratory tests that may not be available, e.g. determination of PaO2. Missing data would result in underestimating the PORT score. Age on the other hand is readily available on all patients.

Recommendation: To address the need to enroll valid patients, we observe that the requirement for basing a primary efficacy analysis on patients with bacteriologic confirmed diagnosis is a major advance (see also the next comment). Enrichment of patients older than 50 year of age will best address the challenge of enrolling of patients for whom a treatment benefit is likely.

The requirements for enrollment could be as simple as the requirements already given in lines 1020-1023: IV drugs should be studied in a population where at least 75% are 50 years of age or older and oral drugs should be studied in a population where 50% are 50 years of age or older.

The enrollment of a subset of patients below the age of 50 is also important. Younger patients do develop CABP and their inclusion would thus create a clinical dataset similar to the ultimate usage pattern of the drug.

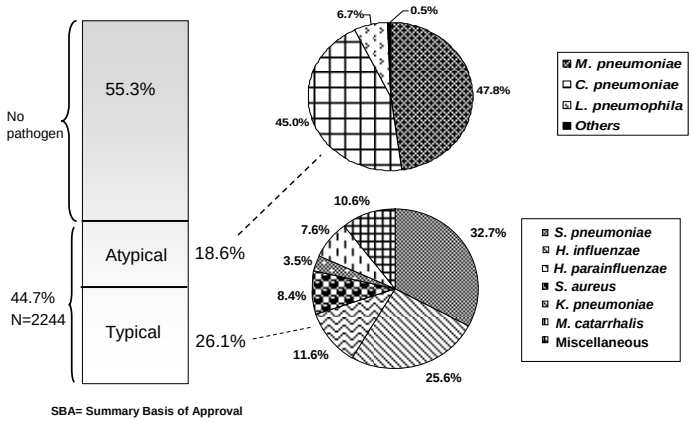
2. **Microbiological ITT (MITT) population as primary population for NI analysis**

As stated in the Draft Guidance at lines 624-6, NI trials must focus on subjects who actually have the disease under study, in this case bacterial pneumonia. In prospective studies where both typical and atypical pathogens were systematically sought, the rate of typical pathogen recovery was 26-34% and atypical recovery was 19-25% (see Figures 1 and 2 taken from Echols RM et al. Clin Infect Dis 2008; 47:S166-S175).

The practical implication of the requirement for a primary or co-primary analysis of a bacteriologic mITT patient population (line 629) will be that the randomized (safety) population will be over 2-fold larger than needed to establish non-inferiority.

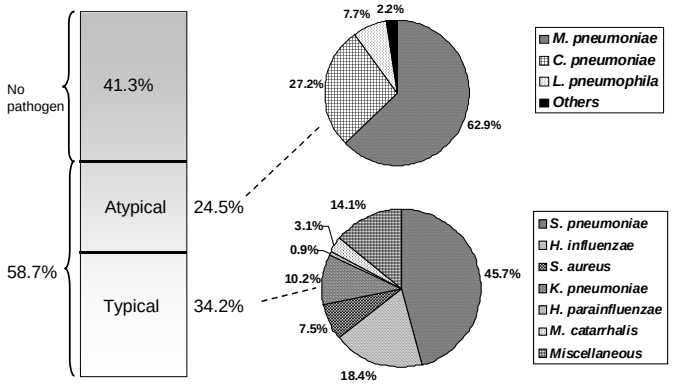
Example: The sample size needed to determine non-inferiority in mild to moderate CAP (10% NI margin; 90% power; alpha 0.05, expected clinical response 85%) is 536 evaluable subjects. If mITT is 40% of randomized subjects, the sample size for one study is 1340 (670 per arm). Two studies would require nearly 2700 subjects.

Figure 1: Etiology of mild/moderate CAP Based on Review of Summary Basis of Approvals- SBA review 1996-2007 (N=5025)



SBA= Summary Basis of Approval

Figure 2: Etiology of mild/moderate CAP – literature review 1996-2007 (N=7428 from 16 publications)



Furthermore, this subset of 30-40% of the microbiologically evaluable subjects is a post randomization set that may lose some of the demographic and disease balance achieved at randomization, and therefore poses a risk for introducing imbalances.

To address these concerns, one could power each of two studies for the ITT or clinically evaluable populations and pre-specify a bacteriologic mITT co-primary analysis by pooling from the two identical or nearly but independent studies.

Recommendation: We recommend that analyses of the Per Protocol (PP) population from each separate study plus a pooled bacteriologic mITT analysis be taken as co-primary

analyses. Meeting formal non-inferiority margins would be required on the PP analyses from the individual studies as well as on the analysis of the pooled bacteriologic mITT population.

3. **Exclusion of patients with any history of prior antibiotics**

The draft guidance recommends against *any* previous antibacterial drug use with efficacy against CABP pathogens prior to enrollment based on data drawn from Pertel PE et al. Clin Infect Dis 2008; 46:1142–51. We believe this broad exclusion is problematic for two reasons:

a) The guideline change is based on an exploratory post hoc analysis of a very limited scope from a single trial.
b) The exploratory observation only applied to antibacterial drugs with greater potency *and* longer half-life (ceftriaxone, levofloxacin, azithromycin, and clarithromycin) and not to drugs with shorter half-lives (penicillins, tetracyclines, trimethoprim-sulfamethoxazole).

The subgroup reclassified as having prior effective therapy is small (less than 100 in each arm), is not powered for comparison to overall treatment, and was not controlled for other factors such as severity of illness. According to Pertel et al., the proportion of patients reclassified as having prior effective therapy (< 24 hours of therapy with both potency and long half-life) was approximately 25% of the overall CE population (26.3% for daptomycin; 24.8% for ceftriaxone). Prior effective therapy consisted predominantly of four different antibacterial therapies in three drug classes. In his commentary on the paper, Powers (Clin Infect Dis 2008; 46:1152-56) was supportive of the overall observation regarding prior effective therapy, but also noted that "*The results of such post hoc analyses may be attributable to chance alone*…".

Prior antibiotics with shorter half life did not influence the outcomes of the treatment arms. The Pertel paper specifically states that the outcomes were similar in patients with prior penicillin therapy (including ampicillin and amoxicillin) and in patients that received no prior antibiotics. Because approximately 50% of the patients received < 24 hours of some antibacterial product prior to enrollment, about 25% of patients received < 24 hours of prior antibacterial therapy with agents such as penicillins, tetracyclines, or trimethoprim-sulfamethoxazole with no apparent effect on outcome.

Thus, the statement in the Draft Guidance that any prior antibacterial treatment will "*reduce the difference between treatment arms and allow an incorrect conclusion of non-inferiority"* is overreaching and will have a strong negative impact on future trials. Too strict an exclusion, such as disallowing any prior antibacterials, will cause CABP trials to be difficult, lengthy, or impossible to execute.

Recommendation: We believe that the official guidance should not drastically rewrite trial requirements based on this single analysis. Reasonable guidance regarding prior antibacterial therapy would allow inclusion of patients with < 24 hours of antibacterial drug therapy with a short half-life within 72 hours of enrollment. The exact list of these drugs needs to be defined, and should include penicillins, tetracyclines, and trimethoprim-sulfamethoxazole.

4. Elimination of atypical pathogens from primary analysis

The proposal to remove atypical pathogens from consideration is contrary to established treatment guidelines. *Legionella* pneumonia is a potentially serious disease associated with risk of mortality and therefore guidelines are needed to obtain a clinical indication for antibacterials that have preclinical activity for *Legionella* spp.

Although infection due to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are accepted as mild, infection due to *Legionella* spp. is estimated to carry an average mortality rate of 10–15% (Edelstein PH & Cianciotto NP, *Legionella* in Principles & Practice of Infectious Diseases, Mandell, Douglas & Bennett [eds], 6th edition, chapter 229). We thus believe that an approach to the study of *Legionella* is needed.

Recommendation: Studies for CAP should be able to enroll subjects with *Legionella* infection. Analysis of the rates of response as part of the overall package and inclusion of the information in the label would seem appropriate. With adequate documentation of diagnosis and clinical response in 10–20 subjects, inclusion of this information in the product label will help characterize new antibacterial agents. If further public comment is required to clarify this point, a workshop regarding the inclusion of atypical pathogens may be helpful.

5. Other comments

1. Line 70: "… and *M. pneumonia*" is inconsistent with the lists on lines 124, 192, and 205. Suggest changing '*M. pneumoniae*' to '*Moraxella catarrhalis*' on line 70.
2. Line 644: "For drugs with only an IV formulation, the MITT population will be considered as the primary analysis population and a 15 percent noninferiority margin is appropriate." Suggest changing 'For drugs with an IV formulation' to 'For drugs with only an IV formulation or drugs with both an IV and oral formulation'.

Summary

The FDA has produced a detailed guidance for CAP for both oral and intravenous drugs. We appreciate the Agency's efforts to assist sponsors in the clinical development of drugs for the treatment of Community-Acquired Bacterial Pneumonia.

New classes of antimicrobials are urgently needed both to address resistance and to provide other options for therapy of emerging infections and biologic threat agents. CAP, now CABP, has been described as the anchor for the development of antimicrobial agents to treat respiratory tract infections, especially for non-hospitalized patients treated with oral agents. Enabling development for use in CABP creates avenues for further exploration of a compound in other settings: both azithromycin and ciprofloxacin provide examples of the benefits that evolution of products in new classes can provide.

We urge the Agency to take these issues into account in developing guidance in this area and trusts these comments will be useful to the Agency as this Draft Guidance is finalized.

Sincerely,

12 June 2009

sanofi aventis
Because health matters

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA–2009–D–0136

Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

Dear Sir/Madam:

Sanofi-aventis U.S. Inc. (sanofi-aventis) welcomes the opportunity to provide feedback on the above-referenced draft guidance for industry, *"Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment,"* and has the following comments:

GENERAL COMMENTS

This guidance is very important given the number of recent public discussions regarding clinical trial design and other issues relating to development programs supporting the approval of antimicrobial products. In light of the emerging levels of resistance, not only in the US but also worldwide, it is critical that new antimicrobial drugs continue to be developed. Overall, the above-referenced guidance is well developed and clear in its objectives.

SPECIFIC COMMENTS:

Lines 69-72: "Common etiologic agents of CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *M. pneumoniae*. Certain respiratory viruses, and atypical bacterial pathogens such as *C. pneumoniae* and *L. pneumophila*, also cause CAP."

Recommendation:

We recommend the following be changed for consistency with regard to the pathogens and in particular, *M. pneumoniae*:

> "Common etiologic agents of CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*. Certain respiratory viruses, and atypical bacterial pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*, also cause CAP."

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Lines 312-314: "Oral antibacterials. Patients being enrolled in oral antibacterial trials should have PORT scores of II or greater. At enrollment, at least 50 percent of these patients should have PORT scores of III or greater."

Comments:

A. Limitations to the Use of PORT Classification

The new CABP guidance will significantly raise the bar for enrolling patients in the ambulatory care setting because of the requirement for higher baseline risk according to PORT criteria and bacteriologic confirmed diagnosis. The impact of these requirements on the enrollment of patients in the ambulatory care setting should be considered.

The PORT Class distribution in the ambulatory patient cohort, as described in the original publication (NEJM, 23 January 1997), was 62% Class I, 26% Class II, 8% Class III, 4% Class IV, and 0.1% Class V. The severity of pneumonia increases with higher PORT Class.

The impact of the proposed FDA guidelines on the eligible patient population may be estimated using this publication as reference. According to the proposed guideline, 50% of patients would have to be PORT Class II (~26% of ambulatory CABP population) and 50% PORT Class III-V (~12% of ambulatory CABP population). That is, about 38% (26%+12%) of the ambulatory population recruited in previous studies would be eligible to enroll. If about 30% of the enrolled population is culture positive (bacteriologic MITT), then only about 11% (38% x 0.3) of the previously eligible patient population in the ambulatory care setting would be in the analysis set.

Under the proposed guidelines, a Phase III study with 90% power, non-inferiority margin of 10%, and an estimated cure rate of 85% will need about 268 bacteriologic MITT subjects per treatment group, according to one estimate. If we assume that 40% of the enrolled ITT patients will have a positive bacterial culture, then 670 patients per treatment group, 1,340 patients for two treatment groups per study, or total of about 2,680 patients (1,340 x 2 studies) will be required from a population that is about 38% the size of what was previously eligible, at a limited number of qualified sites.

The use of PORT classification may not be optimal. The use of PORT scores to guide enrollment is explained (lines 1011-1028) as a way to ensure an adequate level of risk in the enrolled population. However, the data demonstrate the strongest driver for severity is age >50 years (Fleming TR, Powers JH. Clin Infect Dis 2008;47:S108-S120, Dowling and Lepper, Am J Med Sci, 1951;222:396-402). A similar contribution of patients age >50 was observed in FDA's Katherine Laessig's analysis of the most recent data (Anti-infective Drug Advisory Committee meeting on June 2, 2009).

To address the need to enroll valid patients, we note that the requirement for primary efficacy analysis of patients with bacteriologic confirmed diagnosis is a major advance. Furthermore, enrichment of patients older than 50 years of age best addresses the challenge of enrolling of patients who will benefit (i.e., demonstrate treatment effect).

The requirements for enrollment could be as simple as the requirements already given in lines 1020-1023: IV drugs should be studied in a population where at least 75% are 50 years of age or older, and oral drugs should be studied in a population where 50% are 50 years of age or older.

B. The Need for Greater Clarity on Requirements for Labeling of Resistant Pathogens

The new guidance should provide an approach to achieving efficacy labeling for the sub-set of resistant bacteria isolated. The challenge for industry is to develop new antibacterials for resistant pathogens, which are usually a relatively small subset in the bacteriologic MITT population. The new guidance should provide an approach to achieving efficacy labeling for the subset of resistant bacteria isolated.

For example, in developing a new antibacterial for penicillin-resistant *S. pneumoniae*, 536 bacteriologic MITT subjects will be enrolled per treatment group, as estimated above (268 x 2 studies). If 40% of these subjects have *S. pneumoniae*, and resistance rates are about 10% (as we have seen in our experience), then only about 21 per treatment group would be resistant (536 x 0.4 *S. pneumoniae* fraction x 0.1 resistant fraction). Will MDRSP and other claims for resistant pathogens be possible with 21 resistant isolates, or will the sample size need to be increased? Clinical superiority of treatment benefit is likely to be difficult to demonstrate with small subset populations.

The objective of including patients likely to have disease and therefore more likely to demonstrate treatment effect is desirable; however, the challenges in enrolling into the studies should also be considered. A vastly higher number of qualified sites will be needed in order to enroll ambulatory patients in order to encourage new antibacterial development. A public commitment should be made by the FDA to work with the pharmaceutical industry and other interested parties to encourage an environment suitable for the enrollment of sicker patients at a significantly higher number of sites.

Sanofi-aventis appreciates the opportunity to comment on the proposed draft and hopes the comments provided are useful in the guidance development process.

Sincerely,

Brian E. Harvey, M.D., Ph.D.
Vice President
Regulatory Policy

AstraZeneca

June 15, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number FDA-2009-D-0136
Response to FDA Call for Comments
Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

Dear Sir or Madam:

Reference is made to the March 20, 2009 Federal Register notice announcing the request for comments on "Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment"

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Cindy M. Lancaster, US Executive Director, Regulatory Affairs, at (302) 885-1348.

Sincerely,

Darci L. Bertelsen /DT

Darci L. Bertelsen,
Regulatory Affairs Director,
Telephone: (302) 886-7355
Fax: (302) 886-2822

DLB

Enclosure

Regulatory Affairs
AstraZeneca LP
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[Docket No. FDA-2009-D-0136]
Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

General Comments

- Comment 1. Please to see that the guidance is moving forward. Overall, the guidance is comprehensive and addresses the main concerns relating to the indication.
- Comment 2. Major change is the focus on bacterial pneumonia. Scientifically reasonable; however, it will have an impact on scope of clinical programs with larger studies and could consequently discourage development investment.
- Comment 3. Since the focus is on microbiologically confirmed population, the microbiological requirements must be clearly described. Specific points that need additional clarification are noted below.
- Comment 4. The focus on "typical" bacterial pneumonia leaves questions on the development requirements of compounds with atypical activity. Atypical pathogens still are major causes of pneumonia and their activity frequently encountered with new compounds.

Guidance for Industry Influenza: Developing Drugs for Treatment and/or Prophylaxis		
Section	**Page or Line Number**	**Comment or proposed replacement text**
IIIA2	Page 4, lines 116-118	Attainment of 30 to 40 percent of bacterial confirmation is a difficult target to achieve based on current diagnostic methods. Will FDA be open to allowing the use of new methods and will this allowance then be included in the guidance?
IIIA3	Page 5, lines 161 and 162	The statement is restrictive and will not allow consideration of other aspects such as prevention of emergence of resistance for dose selection. AstraZeneca acknowledges that prevention of emergence of resistance is a new and evolving concept, but one that should be allowed to be explored. Suggest to change: "and can ensure that excessive doses (beyond those that add to **overall benefits** ~~efficacy~~) are not used, offering some protection against unexpected and unrecognized dose-related toxicity"
IIIA5	Page 6, lines 202-206	Will HABP and/or VAP trials support the CABP indication? More specifics on this in the document would be helpful, as sponsors may considered 1 or 2 HAP/VAP and 1 CAP trials to obtain both.

Guidance for Industry Influenza: Developing Drugs for Treatment and/or Prophylaxis		
Section	**Page or Line Number**	**Comment or proposed replacement text**
	Page 8, line 301	It is not clear at this time whether the PORT score is acceptable to other agencies. For example, in Europe, CURB-65 may be preferable. In fact, the BTS CAP guidelines classify severity based on CURB-65 (ref. BST CAP guidelines, 2004 and draft 2009). It would be helpful to Sponsors if this were harmonized; if harmonization is not possible, flexibility from both the FDA and EMEA will be needed.
	Page 9, lines 321-332	It is not clear what the purpose of microbiological criteria is. Is it for inclusion of patients? Is it determination to whether specimen should be cultured? Or whether the specimen is valid? Would this be considered in defining whether a patient has a microbiologically confirmed pneumonia? Please clarify.
	Page 9, lines 335-339	Please clarify if the Gram stain criteria can be applied to endotracheal aspirates or BAL or non-sputum specimens?
	Page 9, line 348	It is unclear what value serotyping will have? AstraZeneca suggests serotyping be made optional.
IIIB8	Page 11, line 420	Suggest to modifying to: "Concomitant **systemic** antibiotic therapy **active against respiratory pathogens** should not be allowed…"
IIIB9	Page 12, line 442	30-day mortality as failure is inconsistent with the endpoint assessments and definition of success. If the TOC occurs at day 14 after start of therapy and patient is alive and signs and symptoms resolved, based on the endpoint definition, it should be considered a success; however, if the patient dies at day 30, the patient can also be considered a failure. Requires clarification, as there are two different fixed endpoints.
	Page 15, lines 609-612	The key is identification of a pathogen known to cause CABP. How would an "appropriate" specimen be used? For example, if *S. pneumoniae* is isolated from sputum and there are more than 10 epithelial cells, would that patient be in the MITT or not? Please clarify.
	Page 16, lines 640-641	Suggest to adding: "Sponsors should justify the noninferiority margin for the proposed trial design and population enrolled, **if deviating from this guidance".**
IIIC2	Page 18, line 715	Would there be any consideration for claims on prevention of emergence of resistance? A comment in the guidance on prevention of resistance claims would be useful.

June 25, 2009

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2009-D-0136, Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia

Dear Food and Drug Administration,

The Food and Drug Administration's recent draft guidance on community-acquired bacterial pneumonia (CABP) is significant step forward from the previous draft guidance, issued in 1998. However, it includes recommendations that contradict established principles of rigorous clinical trial conduct, as defined in the International Conference on Harmonization documents E-9 and E-10, and a number of issues are left unaddressed. The recommendations for the conduct of noninferiority trials are most problematic and of greatest relevance, as nearly all recent clinical trials for CABP have been noninferiority trials.

1) Endpoints

"Resolution of signs and symptoms" (lines 433-434) is an inappropriate primary endpoint, as it represents a composite of biomarkers rather than something of clear relevance to patients. A well-validated patient-reported outcome (PRO) tool may be used as an endpoint in a superiority trial for CABP, or mortality.

On the other hand, a noninferiority comparison can be made only when substantial and reproducible evidence for an effect size of an active comparator has been demonstrated. The draft guidance clearly states that for bacterial pneumonia due to atypical pathogens (*M. pneumoniae, C. pneumonia, or L. pneumophilia*) and for viral pneumonia, this evidence does not exist. In pneumococcal pneumonia, both penicillin and sulfa result in a reproducible and compelling reduction in mortality, especially in patients over the age of 50 or with bacteremia. For a noninferiority comparison to be valid, the outcome on which a margin is based must be the same outcome for which an effect size for the active comparator has been demonstrated, and in a study population with similar characteristics as those from the historical data. For CABP, this outcome is mortality.

Therefore, it is troubling that the draft guidance (lines 773-784) argues that a treatment effect for a reduction in mortality with antibiotics can be extrapolated to a "clinical outcome." This is neither logical, nor based on sound scientific reasoning. A noninferiority margin based on a clinical outcome other than mortality can be justified only if compelling evidence of an effect size for this outcome were available, but such data do not exist. Of note, a reduction in fever,

which is a biomarker and not a relevant clinical outcome, does not comprise a valid clinical outcome.

2) Size of Margin in Noninferiority Trials

The draft guidance (lines 796-944) provides an excellent review of the uncontrolled observational and historical data establishing an effect size for antibiotics in reducing morality in patients with CABP. From this analysis, the lower bound of the 95% confidence interval for the effect size of antibiotics (M1) is 15-22%, in patients with pneumococcal pneumonia and a high incidence of bacteremia. From this M1, it is unclear how the FDA justifies an M2 of 15%, which essentially preserves none of the treatment effect of antibiotics. In other words, an experimental antibiotic could be declared "noninferior" when, in fact, it is only marginally better than placebo, and substantially worse than an active comparator. While M1 is calculated from historical data, M2 is determined by clinical reasoning, and it is impossible to justify approval of an antibiotic that is as much as 15% worse in preventing death than an existing therapy. For very ill patients – those over the age of 50 with bacteremia –a margin of at most 10% can be tolerated. In studies with less-ill patients, only smaller margins can be tolerated, or superiority trials must be conducted.

3) Study Population

A common feature of most contemporary trials in CABP is the low rate of microbiologic confirmation of the presence of typical pathogens, suggesting a high rate of atypical and viral pneumonias, and the inclusion of patients who are not very ill. This is not particularly problematic in a superiority trial, because including patients without the disease in question or who are not ill generates bias towards the null finding, making Type 1 error unlikely. Likewise, the "assay sensitivity" of the trial, or the ability of the trial to detect a difference between the experimental drug and an active comparator or placebo is assured by a positive finding. However, including such patients in a noninferiority trial reduces the ability of the trial to identify a treatment difference between the experimental drug and the active comparator, reducing the assay sensitivity of the trail. Unlike in superiority trials, assay sensitivity in noninferiority trials is not assured by a positive finding of noninferiority. Rather, it is an un-testable assumption and it is preserved only through rigorous trial design and conduct. In other words, enrolling patients without pneumonia and who are not ill in a noninferiority trial may lead to scenario in which no treatment difference is observed in the study population, while in patients at higher risk of death – the elderly and those with bacteremia – the experimental treatment may be substantially worse.

Thus, the draft guidance's recommendation that at least 75% percent of patients be over the age of 50 (lines 1020-1021) and that no more than 25% of patients have a PORT score of II or lower (lines 307-310) in a noninferiority trial are appropriate. In contrast, the recommendation that only at least 30-40% of patients have bacteriologic confirmation of typical pathogens (lines 115-118) is insufficient. Rather, all patients in a noninferiority trial must have microbiologic confirmation of a typical pathogen through culture, serology, or antigen testing. Otherwise, the margin established from the historical data, which almost without exception included patients with clear radiographic findings of lobar pneumonia or microbiological evidence of streptococcal pneumonia, cannot be used and a noninferiority comparison cannot be justified.

4) Prior and Concomitant Antibiotic Therapy

Similarly, the inclusion of patients who have received prior and concomitant antibiotic therapy diminishes the ability of a noninferiority trial to detect a differential treatment effect between an experimental drug and an active comparator, reducing the assay sensitivity of the trial and biasing the results toward a positive finding of noninferiority. Not only must this be avoided (lines 410-425), as the draft guidance recommends, but patients with prior antibiotic therapy should not be randomized and concomitant therapy must be absolutely prohibited. On the other hand, prior or concomitant therapy in a superiority trial creates bias toward the null finding of no difference, and can be allowed.

5) Exclusions Based on Post-Randomization Events

In most contemporary trials of CABP, a large number of patients are excluded from analysis because of premature discontinuation of therapy, "intercurrent illnesss," use of non-study antibiotics, and other protocol violations. This must be absolutely prohibited, as a high rate of exclusions based on post-randomization events results in an effective loss of randomization, turning a randomized clinical trial into a mere observational study. Often, these exclusions are imbalanced between the two treatment groups, creating the potential for systematic bias.

6) A Recent Example: Cethromycin

The antibiotic cethromycin (New Drug Application 22-398), which was discussed by the Anti-Infective Drugs Advisory Committee on June 2, 2009, highlights all of the problems that I have identified above. Although the two Phase 3 noninferiority trials comparing cethromycin to clarithromycin in CABP followed most of the principles detailed in the updated draft guidance, they were wholly incapable of demonstrating noninferiority and, even worse, may have obscured that the drug is actually worse than clarithromycin, based on a sensitivity analysis conducted by the FDA. Specifically, these trials enrolled few patients with microbiologic confirmation of typical pathogens (one-quarter), most patients were at low risk of complications and death (1% with bacteremia and half with PORT score of 1), prior and concomitant antibiotics were allowed, many patients were excluded based on post-randomization events, and mortality was not evaluated as the primary endpoint. My testimony before the advisory committee detailing these problems is attached as an appendix.

7) Conclusion

Most of the concerns detailed above are specific to noninferiority trials, which comprise the vast majority of contemporary trials in CABP. The many problems with the design and conduct of noninferiority trials may lead to an incorrect conclusion of noninferiority, a type 1 error, when an experimental treatment is actually substantially worse than a comparator drug. A positive finding from a noninferiority trial only provides reassuring evidence that an experimental drug is better than placebo and not substantially worse than an active comparator when the trial has been conducted rigorously.

Protests from sponsors that the rigorous conduct of noninferiority trials is not feasible are wholly inappropriate, and the scientific principles that provide the foundation for efficacy comparisons should not be bent to accommodate them. Otherwise, there is a real possibility that a new antibiotic will be approved when it is, in fact, worse than existing treatments. This does not serve patients well and it contradicts the public health mission of the Food and Drug Administration. Furthermore, allowing sponsors to conduct noninferiority trials in this fashion does not serve sponsors well, as time and money are wasted on trials that have little capacity to demonstrate efficacy.

To summarize, the only acceptable endpoint on which a noninferiorty margin can be established is mortality, and a margin (M2) of greater than 10% is clinically unacceptable. Validated PROs may be used in superiority comparisons. In addition, noninferiority trials must not allow prior or concomitant antibiotic therapy, exclusions based on post-randomization events, or the enrollment of patients without a confirmed diagnosis of bacterial pneumonia with typical pathogens.

Sincerely,

James Floyd, M.D.
Researcher
Public Citizen

CENTER FOR MEDICAL CONSUMERS

CANN COMMUNITY ACCESS NATIONAL NETWORK

Consumers Union Nonprofit Publisher of Consumer Reports

GAP GOVERNMENT ACCOUNTABILITY PROJECT

NRC FOR WOMEN & FAMILIES

June 18, 2009

Dr. Janet Woodcock
Director of Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857
Fax: (301) 827-3410

Re: [Docket No. FDA-2009-D-0136] Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

Dear Dr. Woodcock:

The current draft guidance for Industry on Community-Acquired Bacterial Pneumonia has many important improvements over the previous draft guidance from 1998. However, there are still some problems that remain, which the Patient and Consumer Coalition strongly urges you to address

1. **Allowing drugs that may be substantially inferior to currently available therapy.**
   The current guidance allows new intravenous drugs, which can be used in patients with serious and life threatening pneumonia, to be as much as 15% less effective than older drugs and still be considered "non-inferior." Allowing such inferiority for new drugs compared to older drugs is clearly unacceptable to patients. We understand that drug companies prefer to perform smaller trials in infectious diseases, including pneumonia, but that would put patients at risk if FDA approves drugs that are substantially inferior to currently available therapies. FDA should accept no more than a 10% loss of effect for any drug in the treatment of pneumonia and preferably 5% or less.

2. **Use of an all-cause mortality endpoint in non-inferiority trials in pneumonia.**
   The historical data support the use of non-inferiority trials in pneumonia; however, these trials only provide useful evidence of safety and efficacy for patients and clinicians if they use the appropriate methodology. These include the same populations, definition of disease, and definitions and timing of outcomes compared to the historical studies that indicate the effect of older antibiotics. The historical data indicate an effect of antibiotics on only one endpoint – all-cause mortality. There are no data to support any other endpoint in a non-inferiority trial and decreasing mortality is obviously the most important outcome for patients. There is no basis for the endpoint that was suggested in the FDA guidance of "complete resolution of signs and symptoms."

3. **Use of mortality and patient symptoms as the outcome measure in superiority trials in pneumonia.**
   FDA should encourage sponsors to develop antibiotics that are superior in safety and effectiveness to those that are already available. Much discussion has surrounded the issue of loss of effectiveness of older drugs due to antibiotic resistance, and this would indicate that we need *better* drugs than those we already have to counter antibiotic resistance. Showing a new drug is "non-inferior" to a drug that is less effective than it was when first approved is not helpful for patients. The endpoint in superiority trials could be a composite endpoint that patients are alive and have improved time to resolution of patient symptoms. Patient symptoms can be measured by use of Patient Reported Outcomes. The Office of Antimicrobial Products should encourage sponsors to use PROs since FDA has released a guidance on the use of PROs in 2006.[1] This methodology can provide a more patient-centered approach to outcomes in clinical trials.

4. **No use of surrogate endpoints in clinical trials of pneumonia and consistent language in the guidance.**
   The current FDA draft guidance correctly states that surrogate endpoints should not be used in clinical trials of pneumonia but then goes on to suggest the use of "complete resolution of signs and symptoms" of pneumonia as the endpoint. An NIH biomarkers definitions working group[2] in which FDA senior officials were participants, articles in the medical literature by FDA senior officials,[3] and FDA's own regulations[4] clearly point out that signs of disease are biomarkers and as such are surrogate endpoints. Physical findings, such as body temperature (which can be affected by drugs like acetaminophen) and what a doctor hears on the lung examination are not valid endpoints in clinical
   trials of pneumonia. As noted above, survival and how patients feel in terms of cough, shortness of breath, chest pain, etc. are the most important outcomes for patients.

   In addition, the FDA draft guidance states that *complete* resolution of symptoms should be the endpoint, but then a footnote on page 11 states that patients may still be coughing but still be considered "cured." It seems obvious that a patient who is still coughing – one of the major symptoms of pneumonia – is not "cured" nor would this represent "complete" resolution of symptoms. The endpoint in clinical trials should measure what it actually states it measures. Switching to another drug based upon a clinician's decision is also a surrogate endpoint since that decision may or may not be based on the patients' symptoms. Rather, the endpoint in trials should be based on patients' symptoms rather than clinician's potentially arbitrary decisions on which drug to choose. If a patient receives another antibiotic because their symptoms are not resolved, it is the symptoms that are most important to measure, not the clinician's decision.

5. **Enrolling patients with sufficiently serious illness in non-inferiority trials.**
   Non-inferiority trials are only valid if they enroll subjects with disease of similar severity to those patients in historical studies. Patients in these historical studies were more seriously ill than patients enrolled in current non-inferiority trials. For example, the recent Anti-Infective Drugs Advisory Committee on the drug cethromycin included a trial that enrolled patients who were not very ill, a population in whom non-inferiority trials do not provide meaningful evidence of

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[1] *www.regulations.gov/fdmspublic/ContentViewer?objectId=090000648045fa90&disposition=attachment&contentType=pdf*

[2] NIH Biomarkers Definitions working group. Clinical Pharmacology and Therapeutics 2001;69(3):89-95.

[3] Temple R. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT ed. Clinical measurement in drug evaluation. New York:John Wiley and Sons. 1995. 1-22.

[4] 21CFR314.500, Subpart H.

effectiveness. Non-inferiority trials in the setting of less serious illness can make two drugs look similar when neither drug is effective. Clinical trials in less seriously ill patients should be superiority trials.

6. **No prior antibiotics in non-inferiority trials.**
   Recent and historical data clearly indicate that prescribing any amount of any antibiotic—even a single dose—prior to enrollment of patients in clinical trials can make less effective drugs look similar to more effective drugs.[5] The practical issues of enrolling patients in trials should not obviate enrolling patients in meaningful trials. There is no reason to enroll a patient in a trial that cannot provide useful results. FDA needs to ensure that investigators who participate in clinical trials are able to follow the protocols and have access to patients early on in their disease to be able to assess their willingness to volunteer for trials prior to receiving antibiotics.

7. **Duration of therapy and oral "switch" in pneumonia trials.**
   Recent and historical data indicate that patients may recover from pneumonia after only a few days of antibiotics and therefore they routinely receive a longer duration of antibiotics than necessary to cure pneumonia. This is a patient safety issue as patients may be exposed to a greater frequency of adverse events for no benefit. FDA should encourage drugs sponsors to study shorter durations of therapy based on time to resolution of symptoms where patients study drugs can be stopped once they are cured. This would also obviate the issue of switching patients to oral drugs, which may expose patients to more risk and also complicates clinical trial designs for pneumonia.

The Patient and Consumer coalition urges the FDA to improve the guidance by resolving the above shortcomings. We cannot emphasize enough that patients should not be put at risk by FDA approvals of drugs that may be substantially worse than currently available therapies, and that mortality is the most important outcome for patients.

Sincerely,

Center for Medical Consumers
Community Access National Network
Consumers Union
Government Accountability Project (GAP)
National Research Center for Women & Families

For more information, contact Paul Brown at the National Research Center for Women & Families at (202) 223-4000 or at pb@center4research.org

[5] Pertel PE et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 2008 Apr 15;46(8):1142-51.

PUBLIC SUBMISSION
As of: November 09, 2009
Tracking No. 809c0810
Comments Due: June 18, 2009

Docket: FDA-2009-D-0136
Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment
Comment On: FDA-2009-D-0136-0001
Draft Guidance for Industry: Community-Acquired Bacterial Pneumonia; Developing Drugs for Treatment
Document: FDA-2009-D-0136-0004
Thomas R. Fleming - Comment

Submitter Information
Organization: University of Washington

General Comment
I am very appreciative to have this opportunity to provide comments regarding the March 2009 draft CABP Guidance for Industry. I would like to begin by discussing five issues of significant concern, and then provide a list of some additional specific comments.

Summary of Significant Concerns

There are five issues that lead to significant concern with the Guidance Document's indication (in lines 429-462) that the primary endpoint of CABP registration trials should be 'complete resolution of signs and symptoms measured at a fixed time point' and (in lines 644-645) that 'a 15 percent non-inferiority margin is appropriate' for drugs with an IV formulation and (in lines 650-651) that 'a 10 percent non-inferiority margin is appropriate' for drugs with an oral formulation.

Issue #1: The proposed primary endpoint, defined by the Guidance to be 'complete resolution of signs and symptoms', is a composite that includes components that are biomarkers. Components that are not direct measures of how a patient functions, feels, or survives are resolution of chest x-ray and physical findings such a sputum color, body temperature and WBC. Effects on this composite endpoint have not been shown to reliably predict effects on mortality. It even is unclear whether such effects reliably predict effects on resolution of symptoms or on reduction of risk of complications. (For example,

use of antipyretics lowers body temperature yet there is no evidence they impact pneumonia related symptoms or mortality; conversely, serum therapy resulted in febrile reactions in 26%-44% of patients, but decreased mortality compared to no specific treatment; see Fleming and Powers. CID 2008; 47:S108-120). Given that the Guidance Document states on lines 228-229 that "Currently, we do not recognize any surrogate markers for clinical outcomes in CABP trials", it is logically inconsistent to accept 'complete resolution of signs and symptoms' as the primary endpoint of CABP trials.

Issue #2: The draft Guidance Document does not acknowledge the important need to look simultaneously within bacteremia and age subgroups when formulating evidence based margins in CABP, if one uses the metric of absolute differences in success rates. On pages S116-117 of Fleming and Powers (CID 2008; 47:S108-120) it is reported that, in 30-49 year olds, the mortality rate in non-bacteremic patients was reduced from 17.84% with no-specific treatment to 7.65% with antibiotics and, in 12-29 year olds, was reduced from 8.69% with no-specific treatment to 2.39% with antibiotics. Hence, even for a mortality outcome, one cannot justify 10% margins in non-bacteremic patients under 50 years of age. This patient population is a substantial fraction of those enrolled in modern day CABP trials. This is of significant importance since mortality data are the only evidence provided in the draft Guidance Document's justification of NI margins for the 'complete resolution of signs and symptoms' endpoint.

Issue #3: Given that mortality is the most clinically compelling benefit provided by antibiotics in CABP and is the only endpoint for which an evidence based NI margin can be formulated, it is not only perplexing that mortality is not the required primary endpoint, but it is even more surprising that it is not even on the list of efficacy endpoints in Section #9 (lines 427-498) of the draft Guidance Document. The reasoning for this might be provided on p. S154 of Higgins et al (CID 2008; 47:S150-156) where it is stated "mortality is not a plausible end point to use in present-day studies of mild-to-moderate CAP" because it so low in present studies (<2%) and since this is a result of the "additional measures taken when therapy is failing" in present-day settings. However, an evidence based justification that such additional measures have meaningfully reduced mortality has not been provided; in fact, there is evidence for the contrary and that mortality in the 1940s and 1950s post the introduction of antibiotics remains similar to that in the present-day setting. First, as noted in Fleming and Powers (CID 2008; 47:S108-120), as in the present day, there were substantial populations of pneumonia patients during the 1940s and 1950s that had mortality in the range of 2% when receiving antibiotics; second, there are present-day populations in the CABP setting where high mortality is observed as noted in the first page of the draft Guidance, (see Ochoa-Gondar et al. BMC Public Health 2008; 8:222); third, as in the present-day setting, rescue therapy was provided in the 1940s and 1950s. Serum treatment and sulfa drugs were used although, as with present day combinations and rescue therapy, there is no evidence establishing this use leads to reduced risk of mortality, (see, for example, Ruegsegger et al. The Ohio

State Medical Journal 1940; 36: 257-261, which shows that serum and sulfa existed, were used and studied singly and in combination before penicillin was used clinically); and fourth, pneumonia is the sixth leading cause of death today, and mortality has not improved since the introduction of antibiotics in the 1940s and 1950s, (e.g., see the slide on mortality by calendar time provided by Wunderink at the CAP AIDAC). Thus, in present-day trials, the lower mortality is due to selection of a population with a low baseline risk of death commensurate with that seen in the historical data. Current data also show it is possible to enroll a cohort of CABP patients having average mortality of at least 15%. In such a setting of higher mortality, the historical data do apply that justify using a 10% evidence based NI margin for the overall mortality endpoint and, as discussed at the FDA/IDSA HAP/VAP Workshop two months ago, it is proper to define a patient to be a success who survives after receiving rescue treatment; i.e., it is proper to use overall mortality as the primary endpoint, where frequency of use of rescue treatment would be a separate secondary endpoint.

Issue #4: There is an unsubstantiated indication in the draft Guidance (lines 638-639) that “non-inferiority margins [for ‘complete resolution of signs and symptoms’] can be justified based on historical evidence of the treatment effect of antibacterial therapy on mortality in patients with lobar or pneumococcal pneumonia.” While the entire Appendix is dedicated to justification of the NI margin in CAP trials, only mortality data are presented. Even though it is known to be treacherous to extrapolate NI margins from one endpoint to another, only weak non-evidence based arguments are provided (lines 775-784, and lines 920-929) for such an extrapolation from mortality to ‘complete resolution of signs and symptoms’. On lines 780-784, the draft Guidance acknowledges the endpoint of clinical failure in a present day trial includes patients who would not have died in the 1940s and 1950s but then, in an apparent non-sequitur, it immediately follows with the strong statement, “Thus, it appears reasonable to include in current trials death, disease progression, and lack of clinical improvement as an endpoint that reasonably well reflects past effects on mortality.” Even if this were true, the statement does not provide a basis for using mortality data to formulate a NI margin for the ‘complete resolution of signs and symptoms’ outcome. At the FDA Anti-infective Drugs Advisory Committee meeting held on April 1-2, 2008 to consider design of registration trials in CAP, mortality was the only endpoint for which an evidence- based NI margin was derived. Furthermore, without providing evidence and using arguments that appear to be invalid based on considerations raised in Issue #3 of this letter, the draft Guidance indicates (lines 920-929) that the treatment effects on clinical cure would be larger than treatment effects on mortality; if this argument were true, it increases doubt about whether treatment effects on ‘complete resolution of signs and symptoms’ would be a surrogate for treatment effects on mortality, the most clinically significant effect of antibiotic treatment of pneumonia. Finally, while the draft Guidance is misleading about the ability to derive an evidence based NI margin for the outcome, ‘complete resolution of signs and symptoms’, it correctly recognizes (lines 456-458) that "an appropriate NI margin has not been defined" for the closely related outcome

‘time to resolution of signs and symptoms’. The lack of evidence upon which to base a NI margin on time to resolution of ‘complete resolution of signs and symptoms’ equally applies to a fixed time point measurement of that same endpoint.

Issue #5: A NI trial is designed to determine whether it can be ruled out that the efficacy of the experimental intervention (EXP) is clinically meaningfully worse than that of a standard of care intervention (STD), the control arm of the trial. The NI margin should be sufficiently small that, by an evidenced-based argument, one can conclude that EXP preserves a minimally acceptable fraction of the effect of STD whenever the trial rules out the NI margin. This minimally acceptable fraction should be based on unbiased clinical judgment regarding how much loss of efficacy (to be allowed by the NI margin) would be clinically acceptable. For example, if a statistically significant 7% or 10% absolute increase in probability of success would be viewed to be clinically relevant, then a loss in treatment effect of 7% or 10% would also be clinically relevant, so the NI margin could not be larger than that. Using ‘M1 & M2’ terminology from the International Conference on Harmonization, even if M1 could be justified to be greater than 15%, how does one justify that M2 does not need to be much smaller than 15%, especially if one argues that the clinical cure endpoint is clinically relevant? Based on experience in 7 recent clinical studies of oral antibacterial drugs for CABP, (see Higgins et al, CID 2008; 47:S150-156) a 15% margin would only allow one to rule out a doubling in the failure rate. As an aside, it is clinically and scientifically inappropriate to choose larger margins than can be rigorously justified, simply to reduce the size of a trial or to increase the likelihood of achieving a positive result, since such an approach allows a substantial risk that current antibiotics providing large benefits on profoundly important outcomes such as mortality could be replaced by meaningfully less effective new antibiotics.

Some Additional Specific Comments

1. (lines 117-118): Why is a target for bacteriological confirmation of the etiologic agent of "greater than 30% to 40%" adequate? This seems to be inconsistent with lines 204-208 of the draft Guidance and inconsistent with the historical evidence.

2. (lines 189-190): Placebo-controlled trials can be done if placebo is added to a standard of care regimen. Examples: add-on designs or trials in patients with resistant pathogens. In fact, a double-dummy NI trial has a “placebo”.

3. (lines 214-220): Given the need to justify the validity of the constancy assumption, and given data suggesting that the oral switch is not necessary with short courses of therapy for pneumonia (see Li et al. Am J Med 2007;120:783-790.), why is it “appropriate to allow oral switch”? Such switching could be providing risk without benefit. Unfortunately, on line 220, the draft Guidance

Document provides an invalid solution to the perception that concomitant medications will compromise the validity of the constancy assumption, specifically by stating: "Clinical assessment should be performed at the time of IV to oral switch."

4. (line 255): The draft Guidance indicates that CABP trials should be double-blinded. Is that patient and evaluator, but not care-giver, or is triple-blinding intended? Later, on line 388, it is indicated that trials should be double-blinded "unless there is a compelling reason for unblinding". If the endpoint is overall mortality rather than ‘complete resolution of signs and symptoms”, concerns with unblinded trials would be substantially reduced.

5. (lines 420-425): The draft Guidance does take a strong position that "Concomitant antibacterial therapy for other infections should not be allowed during the trial until after the test-of-cure visit." On the other hand, the draft Guidance takes the unfortunate position that patients receiving such therapy should be called failures in the ITT analysis and should be excluded from the evaluable population, and that all patients receiving rescue antibacterial therapy should be considered treatment failures. Related discussion is given in lines 531-542. If ‘drug switch’ is allowed to become the endpoint, the trial’s primary outcome measure becomes a surrogate since clinicians base drug switch decisions on biomarkers. Exclusion of such patients in the evaluable population results in significant loss of integrity of randomization. Patients should not be excluded from the analysis based on post-randomization events.

6. (lines 593-594): This line should be revised to read, "The trials should provide high statistical power to detect clinically meaningful treatment effects."

7. (lines 609-614): The MITT population, called the preferred population for NI analyses on lines 629-630, is correctly noted to include all patients who have a baseline bacterial pathogen known to cause CABP. Unfortunately, the draft Guidance appears to consider this criterion to be satisfied if patients in this subset are called failure for reasons such as initiation of concomitant medications.

8. (lines 752-763): The draft Guidance Document properly recognizes several factors that compromise the validity of the constancy assumption, including patient differences, differences in trial conduct such as use of blinding, improved concomitant medications, and changes in the spectrum of bacterial pathogens.

Thank you for your consideration of these issues.

PUBLIC SUBMISSION

As of: November 09, 2009
Tracking No. 8092f872
Comments Due: June 18, 2009

Docket: FDA-2009-D-0136
Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

Comment On: FDA-2009-D-0136-0001
Draft Guidance for Industry: Community-Acquired Bacterial Pneumonia; Developing Drugs for Treatment

Document: FDA-2009-D-0136-0003
David Shlaes - Comment

Submitter Information

Organization: Anti-Infectives Consulting

General Comment

This Draft Guidance should be revised. The requirement to conduct clinical trials of an oral agent in CAP to a 10% NI margin for the microbiologically documented population will essentially guarantee that no such drugs will be developed in the future. In this way, FDA has effectively barred Americans from potential new oral therapies for CAP.

PUBLIC SUBMISSION

As of: 10/6/11 4:07 PM
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Docket: FDA-2009-D-0136
Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

Comment On: FDA-2009-D-0136-0002
Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment; Draft Guidance

Document: FDA-2009-D-0136-0012
David Shlaes - Comment

Submitter Information

Organization: Anti-Infectives Consulting

General Comment

One way forward

1. The effect of antibiotics on clinical resolution at day 3 is so large, that a trial with that as its endpoint could easily justify a 15% NI margin. That change alone would allow greater feasibility for an oral drug.
2. If, in addition, the MITT population could be pooled across two trials, the trials become feasible.
3. Finally, if one could use validated, investigational molecular tests, such as the PCR assay utilized by the CDC, the population could be enriched enough that, in the context of a 15% NI margin, you might not even have to pool the populations across two trials. The issue would be to find out what effect this would have on the ultimate label if any.

CEREXA

A subsidiary of Forest Laboratories, Inc.

0010 9 AUG -3 A9:13

31 July 2009

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2009-D-0136, 20 March 2009 (74 FR, 11963-11964)
Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

Dear Madam/Sir:

Cerexa appreciates the opportunity to provide belated commentary on the above referenced draft guidance. It is Cerexa's intent to provide constructive remarks to assist the FDA in creating a guidance document for industry with specific and transparent expectations for the development of antibacterial drugs. The final guidance should enable robust clinical studies that not only meet FDA requirements, but studies that are also generalizable to other global health authorities and medical practice guidelines. These considerations will be of benefit to industry Sponsors for continuing the global pursuit and investment in antibacterial drug development programs, and ultimately provide meaningful data for treating physicians and the patients in their care.

Cerexa Inc., a wholly-owned subsidiary of Forest Laboratories, is a biopharmaceutical company focused on developing a growing portfolio of novel anti-infective therapies for the treatment of serious and life-threatening infections. Therefore, in support of this intended guidance document, Cerexa provides the following comment:

General Comments:

Proposed primary endpoint population - microbiological ITT:

The use of the mITT as a primary population with a required pathogen recovery rate of 30-40% for each clinical study is extremely difficult - particularly with the exclusion of atypical organisms - and poses numerous practical and ethical considerations. In recent clinical studies conducted by Cerexa in which a rigorous, systematic microbiological sampling approach was followed for all PORT III and IV patients, the pathogen recovery was approximately 30% in each treatment arm from 2 pooled trials. This number is inclusive of patients with an atypical organism plus a typical CABP pathogen. The pooled pathogen recovery number excluded approximately 12% of subjects with only atypical infections, as the study treatment was a cephalosporin with no atypical bacterial coverage. Therefore, the implications of this proposal include the need to dramatically increase patient numbers, expand

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study sites, and lengthen enrollment time, all making such studies impractical for industry to consider undertaking. Furthermore, the inclusion of only those patients with a confirmed pathogen could ultimately lead to treatment arm imbalances, as well as selection bias. It should also be noted that the majority (~70%) of patients meeting criteria and requiring medical treatment for CABP will now be excluded from the primary endpoint analysis. **Recommendation:** There is need for compromise between the NI margin historical population and the reality of empiric therapy for CABP treatment in clinical practice. Specifically, the NI margin rationale can be extended to historical populations of non-pneumococcal or culture negative lobar pneumonia. The most medically relevant co-primary endpoint populations are the per-protocol and ITT in which clinical signs and symptoms and radiographic evidence are appropriate for study inclusion. It may be anticipated, however, that an overall pathogen recovery rate of ~25-30% (inclusive of atypicals) is required. The use of a microbiological ITT and ME population should be considered secondary endpoint populations for the individual trials. One larger study may be feasible with the microbiological ITT and ME populations, but two statistically powered studies would be prohibitive with the current technologies for pathogen identification that are available.

Proposed removal of atypical organisms:
The proposed removal of atypical organisms, one of the most common groups of bacterial CABP pathogens, is impractical and inconsistent with medical treatment guidelines in the setting of empiric therapy for approximately 70% of subjects with CABP. *Legionella pneumonia*, for example, can be a serious infection and is associated with a high risk of mortality[1], particularly in a setting of delayed appropriate therapy[2]. As such, global expert medical organizations such as Infectious Disease Society of America (IDSA)[3], American Thoracic Society (ATS)[1], Canadian Thoracic Society (CTS)[4], and British Thoracic Society (BTS)[5] have proposed suitable empiric antimicrobial coverage in CABP treatment regimens, even among patients who are hospitalized with moderate to severe CABP. From a study design perspective, removal of these patients and/or prohibiting atypical antimicrobial coverage creates numerous ethical, as well as practical issues, and would require clinical trials to be performed in regions that do not adhere strictly to accepted practice guidelines. **Recommendation:** An approach to the study of atypical organisms for both in- and out- patient settings is needed. Given the current global medical practice employing empiric coverage requirements in CABP, patients with atypical infections should be included in clinical trials and suitable antimicrobial coverage should be allowed. In addition, the proposed overall microbiological procurement rate should be inclusive of atypical organisms.

[1] Nolan TJ and McCormack DG. Intensive Care Unit Management of Pneumonia, Chapter 12. In Community–Acquired Pneumonia, edited by Marrie TJ. 2001. p 195, ISBN 0-306-46432-2
[2] Heath CH, Grove DI et al Delay in appropriate therapy of Legionella pneumonia associated with increased mortality.Eur J. Clin Microbiol Infect Dis. 1996 Apr; 15(4): 286-90..
[3] Mandell LA, Wunderink RG et al . Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. CID 2007:44 (Suppl 2) S27.
[4] Mandell LA, Marrie TJ et al. Summary of Canadian Guidelines for the initial management of Community acquired pneumonia: an evidence based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. Can Respir J 2000 Vol7:No5 Sep/Oct.
[5] Macfarlane J. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. Thorax 2001 56(Suppl 4):iv1-iv64 December.

No prior antibiotics therapy:
The proposal to prohibit prior antibiotic therapy is difficult due to the requirements of the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) and the care measures mandated by Health and Human Services (HHS) and Medicare[6] in which antibiotics are expected to be given to pneumonia patients within 6 hrs after hospital arrival. Thus, this proposal poses ethical and practical issues, particularly in the US, when designing a trial that will meet regulatory and medical practice criteria. This will further limit site participation, study feasibility and ultimately patient enrollment from the US. **Recommendation:** Compromise is needed between the NI margin assumptions and the clinical practice reality of empiric therapy for CABP treatment. Allowing a single dose of a short acting antibiotic should be considered since this would theoretically be performed prior to study entry and occur in both treatment arms. Alternatively, a minimum number of subjects with no prior therapy could be required. Finally, patients receiving prior antibiotics should not be excluded (per the proposed exclusion criteria), particularly if the presence of pathogens is confirmed, and regardless of resistance to the prior therapy.

Other Comments on Proposed General Study Considerations (Section III):
Proposed patient stratification using PORT score: The PORT classification system was not developed as a severity score and contains laboratory tests (such as PaO_2) that are either unavailable or unattainable at study entry resulting in incomplete data and an underestimate of the score. Data from experts[7][8] and the FDA[9] have demonstrated that the best predictor for severity is age >50. Additionally, although it is also not a pneumonia severity scoring system, CURB-65 is a reliable, more user-friendly score that could be used for stratification purposes and has acceptance from IDSA, ATS and BTS. If the PORT score is used to assess severity, a reasonable option may be to state a minimum requirement for subject (ex. PORT $\geq$3), but also allow enrollment of subjects with other important markers of severity (hypoxia, ICU admission, hypotension, bacteremia, etc).
Signs and symptoms: If any 3 of the proposed signs and symptoms are accepted, it is plausible that someone with cough, chest pain and dyspnea would be enrolled and these alone do not substantiate severity. As the severely ill patient is the basis for the NI study assumptions, either a fever or elevated WBC should be considered as a requirement.
Clinical outcome: The primary clinical outcome based on complete resolution of signs and symptoms is not appropriate. Most often symptoms do not completely resolve until many weeks after the EOT. As such the following is suggested "resolution of signs and symptoms such that no further antibiotic therapy is required".
Antibiotics post EOT as a reason for failure: Patients receiving other antibiotics for non-pneumonia indications should not automatically be deemed a failure in the ITT or MITT populations. Particularly if the antibiotics are taken after clinical outcome determination had been made at EOT. Post therapy, antibiotics could not be expected to prevent other infections.

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[6] US department of Health and Human Services. Hospital Process of Care Measures for Pneumonia; at http://www.hospitalcompare.hhs.gov/Hospital/Static/InformationforProfessionals_tabset.asp?activeTab=1&Language=English&version=&subTab=8#Pneumonia retrieved 24 July 2009.
[7] Dowling and Lepper, The Effect of Antibiotics (Penicillin, Aureomycin and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with other Methods of Therapy,Am J Med Sci, 1951; 222:396-402
[8] Fleming TR and Powers JH Clin Infect Dis 2008; 47:S108-S120
[9] Dr. Katherine Laessig's presentation Anti-Infective Drug Advisory Committee meeting; 2 June 2009

Development of complications as a reason for failure: Complication development does not fully constitute a reason for failure since these are frequently observed, and often missed during the initial days of therapy in severely ill CABP patients. For example, pleural effusion is very common (up to 40% of CABP subjects) and usually, if small in size, does not alter therapy or outcomes. It is suggested that any patient with a complication that occurs after 48 hrs of therapy would be considered a failure. Interventions for the complications should be considered as part of adjunctive therapy, and patients should be evaluated according to the predefined outcome criteria.

Cerexa appreciates the opportunity to comment on the proposed draft. We hope the FDA finds the comments useful for finalizing the guidance process.

Sincerely,

Steffany Gaffagan
Sr. Manager, Regulatory Affairs

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Recommendations to FDA for Interim Endpoints for Clinical Trials in Community-acquired Bacterial Pneumonia

Foundation for the National Institutes of Health Biomarkers Consortium Project Team

CABP Docket ID: FDA-2009-D-0136

Contents

0 Executive Summary

During recent decades, the efficacy endpoints for Community-Acquired Bacterial Pneumonia (CABP) registrational studies relied on a clinical assessment of cure requiring "complete resolution of signs and symptoms" based on a combination of non-standardized physician-based observations and comments collected from the patient by the physician as well as on the investigator's assessment of the need for alternative antibiotic therapy. As non-inferiority clinical trial design advanced during the late 20th and early 21st century, it became apparent to the FDA and others that the development of more readily quantifiable, reproducible, and externally verifiable endpoints would improve the design of present-day non-inferiority clinical trials for CABP.

In developing updated approaches to endpoints, it was also recognized that outcome measures used for studies that support drug registration for CABP must be relevant for clinical practice. Although the level of detail and accuracy in measurement needed in the setting of clinical trials may differ from that needed in clinical practice, a description of the pivotal (Phase 3, or registrational) clinical trials as conducted is an integral part of the prescribing information and must be based directly on the trial data as collected and analyzed. The choice of primary endpoint for a trial may thus need to balance a variety of competing demands.

In parallel discussions of the design of studies for skin infections, the idea arose that standardized assessments of patient response in CABP in the first few days of therapy might provide key insights into both drug effect and options for trial design (Food and Drug Administration 2010). Consequently, and at the request of FDA, in early May, 2010, the Foundation for the National Institutes of Health (FNIH) convened a Project Team for a Biomarkers Consortium Project entitled "Developing Endpoints for Clinical Trials of Drugs for Treatment of Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia (Phases 1 and 2). The Project Team membership included broad participation from NIH, FDA, the academic research community (including members of the Infectious Diseases Society of America (IDSA)), and interested biopharmaceutical companies.

This document summarizes the work of the Biomarkers Consortium Project Team. Over a series of meetings the group reviewed the available historical and modern data and found that progressive improvement in four symptoms (cough, dyspnea, chest pain, and sputum production) during the first 4 days of therapy was sufficiently well documented that an early response endpoint measure could be proposed. To assess durability of response and other late events, supportive information should be obtained by assessing outcomes at a fixed timepoint after therapy has been completed. Such information could include a late response endpoint similar to the traditional test-of-cure endpoint. Although based on limited data and requiring further research, an early response endpoint can be used to anchor a non-inferiority trial for this indication. The early response endpoint is thus suggested for possible use by FDA in review of registrational trials and approval of applications in CABP while further research into this area is conducted.

1 Introduction/ Background

1.1 Background

Long known as the "Captain of the Men of Death," Community-Acquired Bacterial Pneumonia (CABP) is a well-recognized and frequent syndrome (Spellberg, Talbot et al. 2008). Pneumonia remains the sixth leading cause of death in the United States and the number one cause of infectious disease-related death. Mortality rates in the pre-antibiotic era were often substantial (e.g., rates $\geq$ 60% were reported in patients $\geq$ 60 years of age) (Spellberg, Talbot et al. 2008), and even higher rates were reported for subsets such as patients with bacteremia (Fleming and Powers 2008). With the availability of effective antibiotics and advances in supportive care, mortality rates in the antibiotic era are reduced but still substantial at 10–20% (Ochoa-Gondar, Vila-Corcoles et al. 2008).

Over the past decades, CABP has often been a key element of the initial registration indication(s) for new agents. Based on early observations that fever (core body temperature elevated above the normal range) in particular tended to resolve in just a few days with adequate therapy (Petersdorf, Cluff et al. 1957; el Moussaoui, Opmeer et al. 2006) vs. an average of 8-10 days (Osler 1910; Bullowa 1937) in the pre-antibiotic era, resolution of fever (elevated core body temperature) as well as the more gradual resolution of pulmonary symptoms was used in many early reports as the basis for judging adequate efficacy. As subsequent antibiotics were introduced, trials relied on a clinical assessment of cure that required "complete resolution of signs and symptoms" based on a combination of non-standardized physician-based observations and comments collected from the patient by the physician as well as on the investigator's assessment of the need for alternative antibiotic therapy.

Approaches to endpoints in CABP that reduce dependence on physician-based observations or patient-based reporting have been considered but have to date been frustrated by practical issues. Mortality could be used as an endpoint in trials of CABP (Fleming and Powers 2008) (Spellberg, Fleming et al. 2008) and overall population mortality (10-20%) is theoretically high enough to support this approach (Ochoa-Gondar, Vila-Corcoles et al. 2008). However, the observed overall mortality rate includes patients who cannot be enrolled (e.g., those who died on or before hospital admission). As a result, the mortality rate of the enrolled patient population in recent trials has been $\leq$ 5%, a figure that is too low to make this endpoint practical (Pertel, Bernardo et al. 2008; Tanaseanu, Bergallo et al. 2008; Tanaseanu, Milutinovic et al. 2009). Placebo-controlled superiority-based designs are also not possible in the study of CABP because of the dramatic mortality and morbidity benefit of antibiotic treatment (Spellberg, Fleming et al. 2008).

Thus, development of new agents for this indication has always relied on active-controlled non-inferiority studies using a clinical assessment of cure. As trials based on this approach have detected inferior agents (Pertel, Bernardo et al. 2008)) and as future trials will of necessity rely on comparative agents approved using this approach, a draft FDA Guidance for non-inferiority studies of CABP in which continued use of this approach was proposed in 2009 (Food and Drug Administration 2009, March).

Recent discussions regarding non-inferiority study design have, however, recognized the importance of improving the design of non-inferiority clinical trials for this indication. First, the "clinical response" endpoints used in prior CABP trials have depended upon a physician-based assessment and may also have included biomarkers that are not on the causal pathway of the disease. The composite of these various measures was left to clinician discretion. The concern is that this approach does not meet the regulatory criterion that endpoints must be "well-defined and reliable." Endpoints must be either direct measures of how a patient functions, feels or survives or properly validated replacement endpoints for such measures in the appropriate context of use. In an effort to improve the strength of evidence when efficacy is evaluated in non-inferiority trial designs, work was thus undertaken to assess the clinical relevance of various endpoints, to better define those endpoints, and as well as to evaluate the optimal timing for the assessment of efficacy in patients with CABP.

An additional particular focus for review was to provide strong estimates of treatment effect size relative to placebo therapy based on well-defined and reliable measures derived as closely as possible from patient-based information and taken at specific points in time. Having reliable estimates of treatment effect size is essential for a non-inferiority trial design. Although the historical evidence outlined above is consistent with a large effect, the available data are limited in that:

1. The endpoints used in the historical trials do not specifically define the variables measured and the reliability of how they are measured, two fundamental components of endpoints for pivotal trials.
2. The data are incomplete and cannot be audited.
3. The data are taken from studies conducted many years ago, so their relevance to the modern clinical setting could be questioned. Since the time of these reports, there have been many changes in medical therapy such as improvements in supportive care and ready availability of antipyretics or anti-inflammatory agents which may alter treatment effects on biomarkers such as body temperature.
4. The data are not well controlled for severity of illness (or its potential to become severe) or baseline predictors of outcomes.
5. Development of biomarkers for use in chronic infections (Micheel, Ball et al. 2010) has led to the recognition that the biomarkers commonly used in acute infection should be evaluated carefully to ensure good linkage to underlying syndrome and evaluation and qualification of their use when used as outcome measures in clinical trials. Although both general biomarkers (core body temperature, heart rate) and disease-specific biomarkers (respiratory rate in pneumonia, erythema in skin infections) demonstrate supportive temporality and consistency, they are consequences of the infection rather than causes of the infection.
6. The data do not provide direct access to patient-based outcomes similar to those used in patient-reported outcome (PRO) tools.

Physicians and patients have a natural interest in the overall outcome at the end of therapy and thereafter — the goal is resolution of the infection, no relapse, no late sequelae, and no significant adverse effects of the therapy itself. The traditional clinical trial Test-of-Cure (TOC) endpoint taken at a time after therapy has completed has had the goal of capturing all of these

elements, but in so doing it has incorporated a subjective decision-making element that makes it ill-defined from a regulatory perspective. Recognition of this potential ambiguity is useful for understanding the role that a novel regulatory endpoint might play in resolution of this problem.

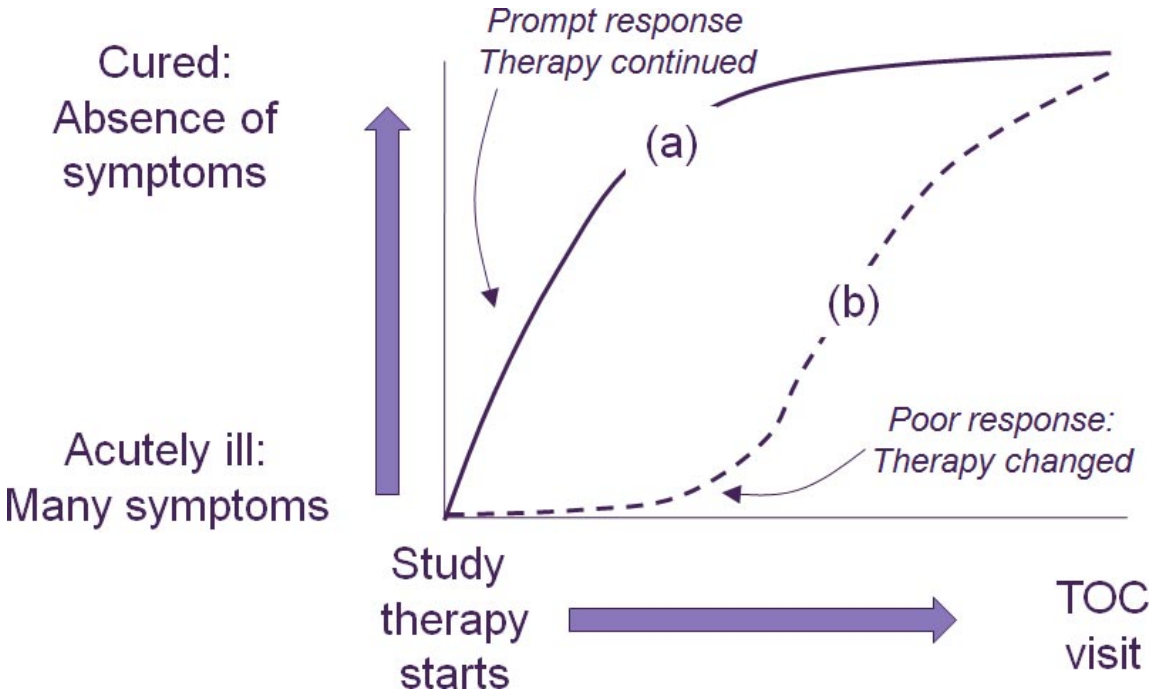
Specifically,

1) The final patient state associated with the *traditional* TOC endpoint of "Cured" was characterized by the complete or near complete absence of symptoms associated with the infection and the return of relevant physiological parameters to normal (or premorbid status). Acceptance of a "near complete" absence of symptoms was justified in part by prior studies that showed that complete return to previous baseline status in CABP may take months, which is longer than the time point at which TOC measures have been obtained (Metlay, Atlas et al. 1998). While clinicians often express confidence in their ability to reliably define and measure near complete absence of symptoms in the setting of clinical practice and thus often consider such an endpoint to be well-defined when taken at a sufficiently late point in time, measures of improvement need to be clearly defined and quantified in the setting of clinical trials.

2) Contributing reasons to the traditional TOC endpoint becoming ill-defined are the incorporation of components that either are not well-defined and reliable or are biomarkers where effects on these measures have not been shown to reliably predict effects on direct measures of how a patient feels, functions, or survives, and the inclusion of events that occur before the TOC endpoint. Although viewed as relevant by patients and physicians, such earlier events contain some subjective decision-making components.
    a) The decision to continue or discontinue study drug therapy, especially during the first few days of therapy.
    b) The decision to utilize salvage therapy.
    c) The observation (or not) of therapy-limiting adverse events.

3) Thus, the patient's state <u>alone</u> at the late time point of the traditional TOC endpoint may not be sensitive to study drug effects. As illustrated in Figure 1, both patients (a) and (b) could be judged as Cured at the TOC visit, but they reach this state in different ways:

Figure 1. Similar outcomes at a traditional late TOC visit, but different courses



New insights around the events that occur early in therapy and the possibility of a new early endpoint can contribute to addressing these problems. The work described in this document provides the basis for a consistent and objective description and documentation of the key early decision-making steps, thereby creating a well-defined approach to endpoints that capture and describe the overall effectiveness of study drug therapy (initial efficacy, sustained efficacy, and tolerability).

1.2 Approach Taken by the Project Team

At the request of FDA, in early May 2010 FNIH convened a Project Team with broad participation from NIH, FDA, the academic research community (including members of the Infectious Diseases Society of America (IDSA)), and interested biopharmaceutical companies to address the issues described above. The group has worked to develop a consensus on alternative primary and secondary endpoints that might improve the quality of future clinical trials of CABP.

In developing updated approaches to endpoints, it was also recognized that outcome measures used for studies that support drug registration for CABP must be relevant for clinical practice. Although the level of detail and accuracy in measurement needed in the setting of clinical trials may differ from that needed in clinical practice, a description of the registrational (Phase 3) clinical trials as conducted is an integral part of the prescribing information and must be based directly on the trial data as collected and analyzed. The choice of primary endpoint for a trial may thus need to balance a variety of competing demands.

It was thus agreed that the approach to developing such endpoints would involve two steps.

First, available data would be used to develop a set of interim recommendations that would permit sponsors to continue development of drugs for this indication (and, consequently, that FDA would consider data based on these recommendations as pivotal data for review of applications for marketing authorization) (Phase 1). Second, a series of investigations would be undertaken into further possible improvements of endpoint measures and/or development of new measures (Phase 2). Such work might well benefit from incorporation of clinical trial data obtained using the interim recommendation endpoints as a starting point. Thus, improvements of endpoint measures would become available in the near future. The recommendations presented here are interim; they are based on currently available evidence, but there is an urgent need for further research to address the gaps in research elucidated during the Project Team's review.

This initiative is particularly important at a time when the incidence of treatment-resistant pathogens is increasing (Boucher, Talbot et al. 2009). The recent slowdown in antimicrobial drug development and lack of clarity regarding regulatory requirements for registration of these important drugs adds further urgency to this undertaking.

2 Summary of Project Team Process

The members of the Project Team convened for a series of meetings during 2010 and 2011. Over the course of these meetings, the group discussed the historical literature, recent publications, and data from several available modern clinical studies. The group developed a consensus on a two-phase process to identify primary and secondary endpoints for ABSSSI (discussed separately) and CABP (this document).

2.1 Phase 1: Retrospective Data Analyses

The goal of this phase was to perform retrospective analyses of datasets from existing clinical studies to a) refine/confirm currently proposed outcome measures by determining how they performed in a modern clinical trial setting; b) help identify additional endpoints or biomarkers that might be relevant. The Project Team has identified several sources of data from existing modern industry clinical trials that have been used as an in-kind contribution to the project.

These analyses, which have also been contributed in-kind to the project, have been based in each case on a statistical analysis plan (SAP) drafted by qualified biostatisticians who are part of the Project Team; each SAP was shared with the entire Project Team for comment and approval prior to initiating the analyses.

2.1.1 Summary of Existing Datasets

1. Historical data
    a. Bullowa, J. G. M. (1937). Chapter II. The course, symptoms and physical findings. The management of pneumonias. New York, NY, Oxford University Press: 36-76.
    b. Finland, M., W. C. Spring, et al. (1940). Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine. J Clin Invest 19(1): 179-99.

c. Flippin, H. F., J. S. Lockwood, et al. (1939). The treatment of pneumococcic pneumonia with sulfapyridine. JAMA-J Am Med Assn 112: 529-534.
d. Meakins, J. C. and F. R. Hanson (1939). The treatment of pneumococcic pneumonia with sulfapyridine. Can Med Assoc J 40: 333–6.
e. Osler, W. (1910). Specific infectious diseases: Lobar pneumonia. The Principles and Practice of Medicine. New York, D. Appleton and Company: 164-192.
f. Wilson, A. T., H. A. Spreen, et al. (1939). Sulfapyridine in the Treatment of Pneumonia in Infancy and Childhood. JAMA 112: 1435-1439.
g. Summary analyses of early antibiotic era data (Presentation by Mary Singer, 8 Dec 2009 FDA AIDAC, available online at www.fda.gov).

2. Pfizer Pharmaceuticals generously provided the primary data tables from the clinical trials which the two comparative studies of tigecycline vs. levofloxacin which underpinned tigecycline's approval for CABP:
    a. Tanaseanu, C., C. Bergallo, et al. (2008). Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. Diagn Microbiol Infect Dis 61(3): 329-38.
    b. Tanaseanu, C., S. Milutinovic, et al. (2009). Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC Pulm Med 9: 44.

3. Cubist Pharmaceuticals generously provided analyses of responses over time in the ceftriaxone arm from a study of daptomycin vs. ceftriaxone for CABP:
    a. Pertel, P. E., P. Bernardo, et al. (2008). Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 46(8): 1142-1151.

4. Both FDA and Cerexa, Inc. generously provided analyses from the two studies of ceftaroline vs. ceftriaxone which underpinned ceftaroline's approval for CABP:
    a. FDA Briefing document for 7 Sep 2010 AIDAC: Ceftaroline Fosamil for the Treatment of Community-acquired Bacterial Pneumonia and Complicated Skin and Skin Structure Infections. Available online at www.fda.gov
    b. Cerexa Briefing document for 7 Sep 2010 AIDAC: Ceftaroline Fosamil for the Treatment of Community-acquired Bacterial Pneumonia and Complicated Skin and Skin Structure Infections. Available online at www.fda.gov

2.1.2 Review of Historical Data

A review of the course of untreated pneumonia provided a useful baseline against which to judge the clinical course of the disease in the modern era and also from which to draw insights into possible endpoints (see material summarized in Section 5.1). Reviews of work by Osler (Osler 1910) and Bullowa (Bullowa 1937) provided illustrations of the typical course of symptoms associated with the syndrome of acute bacterial pneumonia, including cough, dyspnea, chest pain especially worsened with coughing, and expectoration of sputum. The patient would experience a steady deterioration during the early course of disease with progressive respiratory symptoms and change in mental status. If the patient survived, the initial sign of resolution would be a

drenching sweat after the eighth or ninth day (the "crisis"). Initial resolution was followed by onset of suppurative complications in some patients.

Based on these data, a critical analysis of the course of illness in the untreated patient can be generated. Early in the course of illness, the untreated patient has fever (elevated core body temperature) and multiple respiratory symptoms. Prior-generation physicians wrote more about elevated body temperature because it was so obvious and because the day of the "crisis" was such an important clinical event. But, it is also clear that respiratory symptoms were prominent and progressive and that they also began to improve once the fever began to resolve. Osler describes this transition well when he writes, "After persisting for seven to ten days, the crisis occurs, and with a fall in the temperature the patient passes from the condition of extreme distress and anxiety to one of comparative comfort." It is thus well documented that in the untreated patient, respiratory symptoms were not improved by day 3-4 but rather that steady deterioration could occur during this period.

These results were contrasted with the experience in the early antibiotic era.[1] Based on data from the early antibiotic era (Flippin, Lockwood et al. 1939; Meakins and Hanson 1939; Wilson, Spreen et al. 1939; Finland, Spring et al. 1940), an antibacterial treatment effect using clinical recovery as an endpoint can be described. As described by early investigators in qualitative terms, the effect was rapid and striking (Flippin, Lockwood et al. 1939): "From the very beginning of this study, we have been impressed, as were Evans and Gaisford (1939), by the striking frequency with which the initiation of drug treatment was followed within 24 hours or less by a critical drop in the patient's temperature. This temperature drop was not immediately accompanied by any significant changes in lung signs but always reflected a marked improvement in the toxemia and the general well being of the patient. Resolution of the pneumonia then followed within a variable period of days".

Using an endpoint characterized by a general improvement in the patient's clinical condition as observed and recorded by the physician, substantial treatment effects can be estimated from these data:

- A quantitative estimate of treatment effect for symptom resolution at 48 to 72 hours is 29% (95% confidence interval = 21-37%) (Finland, Spring et al. 1940).
- A quantitative estimate of treatment effect for clinical recovery at day 3 is 72% to 77% (Bullowa 1937; Flippin, Lockwood et al. 1939; Meakins and Hanson 1939).
- Quantitative estimates of treatment effect for mean days to clinical improvement, fall in temperature, and clinical recovery were 2.5, 3.4 and 4.2 days, respectively (Wilson, Spreen et al. 1939).

Although these data suggest a significant effect of antibacterial agents, the data also have a number of limitations:

- The data are mostly observational or from small studies.
- Cross-study comparisons were used to determine treatment effect.
- The endpoints not clearly defined, but were clinically reasonable.

[1] Data adapted from a presentation by Mary Singer, 8 Dec 2009 FDA Anti-Infective Drugs Advisory Committee.

But, the studies also have counterbalancing strengths (they were contemporaneous; except for Finland's 1940 study (Finland, Spring et al. 1940), mortality rates ranged from 3-7% in treated patients and were thus similar to mortality rates reported in contemporaneous controlled studies; the data were primarily from cases of pneumococcal disease). Taken together, this collection of pre-antibiotic and early antibiotic era data suggested a significant treatment effect at approximately day 3–4 after initiation of therapy. On this basis, an exploratory, hypothesis-generating analysis was undertaken of the tigecycline-levofloxacin CABP dataset in an effort to better define the variables measured in the "clinical response" endpoint.

2.1.3 Tigecycline vs. Levofloxacin - Hypothesis Generation

In this phase of the work, data from the two pivotal trials underpinning the registration of tigecycline for CABP were analyzed (Tanaseanu, Bergallo et al. 2008; Tanaseanu, Milutinovic et al. 2009). These studies enrolled patients with an average age of 51 years with a distribution of PORT scores (I-V, microbiologic modified ITT [intention-to-treat] population) of 22%, 31%, 27%, 19%, and 1%. In both studies, tigecycline was compared with levofloxacin as monotherapy for CABP. Patient-level data on the time course of four symptoms were available for analysis. Specifically, scores of absent, mild, moderate, or severe had been recorded for each of these four symptoms:

a. Cough
b. Pleuritic chest pain
c. Dyspnea
d. Sputum production

Based on the idea that rapid symptom improvement might be expected early in the course of therapy (but not necessarily complete resolution over such a short period of time), a series of exploratory initial analyses focused on three possible definitions of response. The first two definitions sought to define the concept of "some symptom better with no other worse," whereas the third definition measures disappearance of all symptoms:

a. The first day when some baseline symptom was better, with none of the other symptoms having become any worse.
b. The first day when some baseline symptom was now absent, with none of other symptoms having become any worse.
c. The first day when all symptoms were reported to be absent.

Further analyses explored two types of "temporary responders", that is, patients with initial response who did not maintain that response. Such patients were defined as either:

a. Patients with a response at Study Day[2] 3, 4, or 5, but with failure to maintain that response at all later times.

Or

[2] Throughout this document, Study Day 1 corresponds to the day of initiation of study therapy. An observation on Study Day 2 (usually the next calendar day) would be taken approximately 24h after initiation of therapy, an observation on Study Day 3 would be taken approximately 48h after therapy initiation, Study Day 4 would be approximately 72h after therapy initiation, and Study Day 5 would be approximately 120h after therapy initiation. The datasets discussed in this paper did not rigidly define specific time windows but rather appear to have followed a largely calendar-day based convention.

b. Patients with a response at Day 3, 4, or 5, but with a failure to maintain the response at the TOC visit.

Finally, the Project Team considered the possibility that endpoints with a stricter response definition might either reduce the problem of "temporary response" or offer a usefully different pattern of response over time. Thus, variant definitions of response along the scale of absent, mild, moderate or severe were also considered:

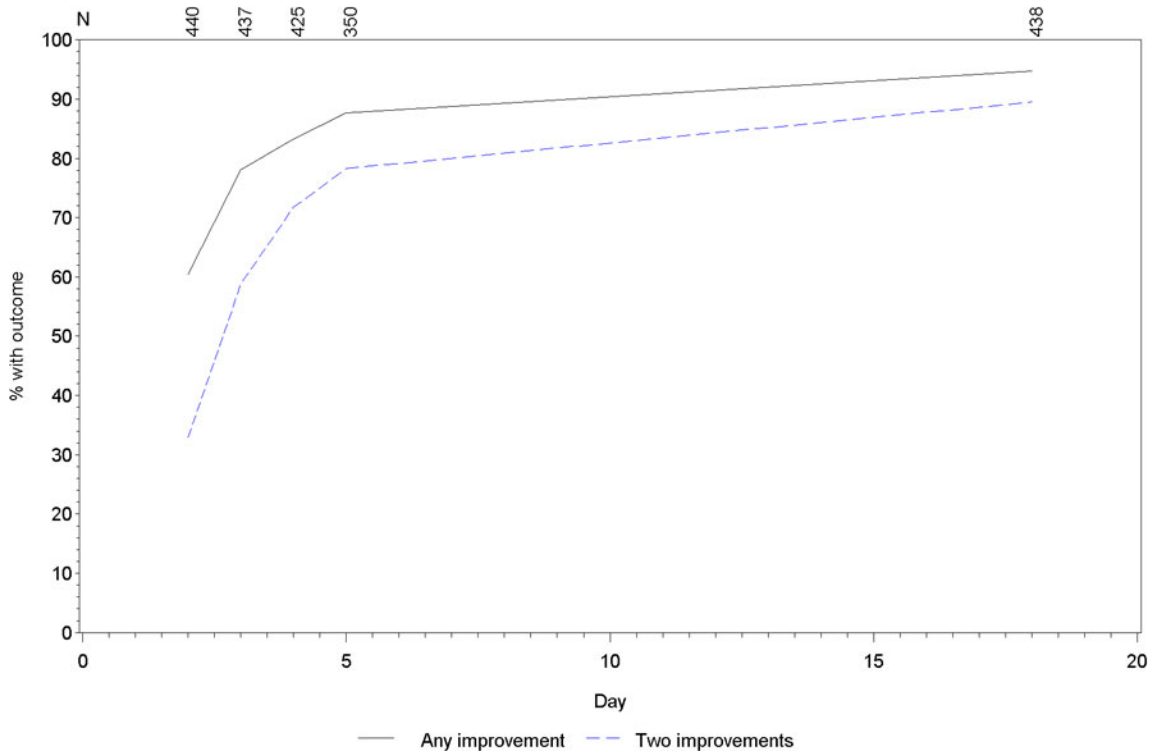
a. Any improvement from baseline in 2 of 4 symptoms, with none of other symptoms having become any worse.
b. A 2-point improvement (e.g. from severe to mild or moderate to absent) in one symptom, with none of other symptoms having become any worse.
c. A 2-point improvement in one symptom, a 1-point improvement (e.g. from severe to moderate or mild to absent) in another symptom, with none of other symptoms having become any worse.

These additional observations were relevant to understanding the available data:

a. Most patients had daily observations and measurements during the first 4 Days of therapy.
b. Subsequently, significant time gaps would span observations and measurements. As the exact Day of a change could not be estimated, missing observations were not replaced by last observation carried forward.
c. Most patients have a TOC and Late Follow-up (FU) data point, but these observations did not occur on the same Day for all patients. Thus, the number of observations on specific Days after about Day 5 becomes quite variable.
d. The highest number of observations was on Days 1-4, at the TOC visit, and at the FU visit.
e. Baseline findings for at least two symptoms (that is, a score of Mild, Moderate, or Severe rather than a score of Absent) were present in 96% of patients (See supplemental data in Section 5.2, Table 6) and thus most patients could be judged to improve based on a two-symptom rule. In addition, 93% of patients had a sufficient number of symptoms to meet a response rule requiring a 2-point change in at least one symptom and 91% had sufficient symptoms to meet a response rule requiring a 2-point change in one symptom accompanied by a 1-point change in another symptom.
f. Although the strength of symptom scores of Absent, Mild, Moderate, and Severe is limited by the lack of well-validated definitions, the Project Team believes that the perception that drives a change in category for an individual patient is likely to reflect a meaningful change in patient status. Further, the short duration of illness is likely to permit reasonable recall.

The core results are shown in Figure 2. In this graph, the y-axis shows the percentage of subjects meeting rules in which response meant improvement in one symptom by one point (solid line) or in two symptoms by one point (dashed line) with no worsening of any other symptom. As can be seen, rapid improvement can be documented during the first five Study Days based on analyses of these symptoms. This result appears similar to the qualitative descriptions of clinical response in the early antibiotic era literature.

Figure 2: Improvement in CAP symptoms over Days 1-5, all patients



To aid with understanding how the new definitions performed in the context of the traditional TOC endpoint, supplemental analyses were performed for the subsets judged Cured vs. Failed at the traditional TOC endpoint (Section 5.2, Figure 4 and Figure 5). These analyses have a number of limitations (principally, they rely on the traditional TOC and its subjective elements which the Project Team seeks to avoid), but they proved useful during consideration (see below) of the choice of rule and time point that produced the least number of both temporary responses and responses that were discordant with the traditional endpoint.

The definition that was determined to offer the greatest merit was the one which required improvement in at least two symptoms, each by at least one point (that is, an improvement by one category such as from Moderate to Mild). As noted above, 96% of patients had sufficient baseline symptoms to permit them to meet the response criterion and the Project Team decided that improvement-in-two-symptom-categories supported a larger treatment effect that would correspond to clinically meaningful effects. Conclusions based on this definition were:

a) The requirement for improvement by at least one point in two symptoms yields improvement rates of 59, 72, and 78% on Days 3, 4, and 5 for all patients combined (Figure 2).

b) Agreement between the response at Days 3–5 with clinical cure/failure as judged at the traditional TOC visit was assessed as a guide to maximizing sensitivity to early treatment effect while also limiting the number of temporary responders (those showing an initial response meeting the rule but with subsequent worsening of symptoms):

i) Broadly, earlier times (Day 3) were better for limiting the number of patients who are an early improver, but are ultimately classified to be a clinical failure at the TOC visit. This conclusion appears biologically plausible but the data on this point are limited by varying numbers of observations on each Day in this small dataset.
ii) Similarly and with the same limitations, later times (Day 5) were better for limiting the number of patients who are an early non-improver, but who were ultimately judged as a clinical cure at the TOC visit.
iii) Reasoning that failing to predict ultimate successful outcome is a lesser error than incorrectly predicting success, earlier times (Days 3-4) overall seemed to offer the best balance.

c) In summary, minimizing the number of patients who improve early and then are not improved later was determined as most appropriate and is facilitated in this dataset by an early evaluation at Days 3 and 4:
i) Improvement rates for ultimate clinical failures were minimized on these Days.
ii) Evaluation on these days minimized the number of patients showing improvement at this time, but not subsequently classed as an improvement.

Two alternatives to the definition requiring a one-point improvement in at least two symptoms were analyzed in parallel, with all three rules shown in Table 1. The Project Team also analyzed the frequency with which an initial response was not sustained as judged by failure to meet the same rule at the TOC visit (Table 2).

Table 1: Response rates for three possible response definitions

Day	One-point improvement in two symptoms	Two-point improvement in one symptom	Two-point improvement in symptom, one-point improvement in another symptom
Day 3	257/437 (59%)	155/437 (35%)	138/437 (32%)
Day 4	305/425 (72%)	209/425 (49%)	193/425 (45%)
Day 5	274/350 (78%)	203/350 (58%)	192/350 (55%)

Table 2: Rates of temporary improvement - Met the response rule at an early time point but not at TOC

Day	One-point improvement in two symptoms	Two-point improvement in one symptom	Two-point improvement in symptom, one-point improvement in another symptom
Day 3	10/251 (4%)	7/149 (5%)	7/134 (5%)
Day 4	8/300 (3%)	8/204 (4%)	7/190 (4%)
Day 5	10/271 (4%)	4/199 (2%)	6/190 (3%)

Overall, the definition of early response requiring a one-point improvement in at least two symptoms overall appeared most consistent with both TOC data and the prior descriptions of antibiotic response. Despite the above-discussed limitations of the TOC endpoint, the Project Team felt that given these evaluations looked specifically at symptom improvement, considering

the correlation of early and late response was an appropriate way to use all of the available information to calibrate the proposed early endpoint rules.

The Project Team discussed at length the merits of the alternative rules. Although the greater stringency of the two-point improvement endpoints might offer greater sensitivity to treatment effects, some members of the Project Team thought these were more difficult to interpret. First, they were concerned that it is not clear what a two-point change means. Second, response rates based on a two-point improvement were lower than seemed clinically plausible. Finally, the one-point improvement concept is similar to the idea of "Any improvement" and might be considered a simpler definition to understand and use.

Finally, all three endpoints had relatively low (<5%) and similar rates of temporary improvement. Discordance rates for only those patients successful at TOC were similar to those above for all patients combined. Discordance rates in those unsuccessful at TOC were difficult to interpret due to low numbers — the absolute number of discordant patients in this group was low.

Based on these discussions, the Project Team concluded that the one-point-improvement-in-two-symptoms rule was a reasonable approach but that alternative rules could be (re)considered and developed as additional data become available.

Conclusions From This Analysis

1) This analysis of the three definitions and the reliability of the early response measure suggest that a one-point improvement in two symptoms at Day 3, 4, or 5 should be the focus of further analysis when symptoms are classified on a four-point scale consisting of absent, mild, moderate, severe.
2) Alternative approaches were possible but were considered to present obstacles that were greater than those posed by the consensus endpoint definition.
3) The two-point improvement definitions included the issue that defining a two-point change is a more challenging hurdle to meet and all two-point improvements may not be equal. Although all one-point improvements may as well not be equal, a one-point improvement could be taken as a meaningful step from the patient's perspective and a pair of such improvements for two different symptoms was likely a strong finding. Future research is needed to better define responder criteria.
4) In addition, response rates based on a two-point improvement were in a range (ca. 50%) that would require substantially larger clinical trial sample sizes than those required for response rates closer to 70–80%. The Project Team discussed the possibility of selecting the rule based on its impact on sample size but could only conclude that further research was required on that point.
5) "Any improvement" could be considered a simpler definition to understand and use.
6) All three definitions of the endpoints had relatively low and similar rates of temporary improvement, so the choice of definition was not a factor in discordance.
7) In terms of the timing of the outcome assessment, Days 4 and 5 had higher response rates with similar levels of discordant responses.
8) No data are available on the content validity or reliability of the scale used in this analysis; however, the analysis of the presented data in this form was used to understand the disease

pattern. Future research would help to evaluate the content validity, understandability to patients and reliability of scales.

a) Although scale reliability had not been validated, it was noted that the short duration of the illness would facilitate accurate day-to-day comparison by the patient and that change in rating level was likely to reflect the course of the illness. The validity of this assumption should be studied in future research.
b) Some members of the Project Team noted that although the use of this scale was appropriate, the terminology for Mild, Moderate, Severe, and Absent needed better and more precise definition.

9) The available data indicated that most patients with CABP receiving effective therapy demonstrate a two-symptom improvement, each by at least one point.

2.1.4 Analysis of Ceftriaxone Treatment Data - Limited Hypothesis Testing

Using the ideas developed from investigation of the tigecycline-levofloxacin analysis, an analysis plan was developed for the ceftriaxone data from the ceftriaxone-daptomycin CABP trial (Pertel, Bernardo et al. 2008):

In brief, two CABP studies were conducted with daptomycin (Cubicin, formerly Cidecin) vs. ceftriaxone. Of these, the first was completed in 2000 and the data from the ceftriaxone arm were generously made available for this analysis. The second study was stopped when the results of the first study's results became available.

In this study, the mean age of the enrolled patients in the ITT ceftriaxone group was 56 years with a PORT Risk Class distribution (I-V) of 0%, 44%, 30%, 27%, and 0% (Pertel, Bernardo et al. 2008). The same four symptoms as previously analyzed (cough, chest pain, dyspnea, and sputum production) were serially recorded for each patient. A weakness of this dataset is that symptoms are only recorded as present or absent. A further weakness is the small number of failures in the ceftriaxone arm. Thus, the exploratory analysis provides only limited hypothesis testing. Although the definition used in the study protocol and presented to investigators was to evaluate "improvement" in symptoms, the case report forms did not conform with this definition since investigators were only offered the choices of "present" or "absent" for each symptom.

Of the evaluable population of 286 patients, 97.6% had two or more symptoms at baseline. Overall, 81.1% of subjects had at least one symptom resolve by Day 4 and 58.1% had at least two symptoms resolve by Day 5 (Table 3). Similar to prior observations (Metlay, Fine et al. 1997), cough took longer to resolve than other symptoms. For example, in the subset of patients with at least one symptom eradicated, only 30% had cough resolved by Day 5, whereas 60, 52, and 66% of patients have resolution of dyspnea, chest pain, and sputum production, respectively (Table 4). A similar pattern was observed in the subset with recorded resolution of at least two symptoms (Table 5).

Table 3. Number of symptoms resolved by Study Day

Study Day	Resolution of at least one symptom	Resolution of at least two symptoms
3	193/286 (67.5%)	67/279 (24.0%)
4	232/286 (81.1%)	127/279 (45.5%)
5	243/286 (85.0%)	162/279 (58.1%)

Table 4. Timing of resolution of at least one symptom

Study Day	N with at least ONE symptom eradicated	Cough eradicated (%)[a]	Dyspnea eradicated (%)[a]	Chest pain eradicated (%)[a]	Sputum production eradicated (%)[a]
3	193/286 (67.5%)	18 (9)	91 (47)	75 (39)	103 (53)
4	232/286 (81.1%)	44 (19)	126 (54)	111 (48)	143 (62)
5	243/286 (85.0%)	73 (30)	145 (60)	126 (52)	161 (66)

[a]Data in these columns show n eradicating the given symptom / N eradicating at least one symptom (%)

Table 5. Timing of resolution of at least two symptoms

Study Day	N with at least TWO symptoms eradicated	Cough eradicated (%)[a]	Dyspnea eradicated (%)[a]	Chest pain eradicated (%)[a]	Sputum production eradicated (%)[a]
3	67/279 (24.0%)	17 (25)	50 (75)	47 (70)	47 (70)
4	127/279 (45.5%)	42 (33)	91 (72)	85 (67)	97 (77)
5	162/279 (58.1%)	71 (44)	114 (70)	106 (65)	128 (79)

[a]Data in these columns show n eradicating the given symptom / N eradicating at least one symptom (%).

Relationship between Symptom Resolution and Clinical Outcome. The sensitivity and the specificity of at least one symptom vs. two symptoms resolved were assessed. To evaluate sensitivity, the cure rates and the percentage of patients who had at least two symptoms resolved were of interest. Of those classified as a cure at the TOC visit, 82% had at least one symptom resolved by Day 4. However, 82% of those classified as a failure at TOC likewise had at least one symptom resolve. On the other hand, 62% of the patients judged to be a cure at TOC had at least two symptoms resolved on study Day 5 vs. only 18% of subjects ultimately judged to be a failure. Once again, such analyses must be interpreted with caution since "cure at TOC" is used as the "gold standard" in such comparisons, even though it has not been established to be a validated surrogate endpoint for long-term resolution of symptoms.

Characteristics of Four Failed Patients with at Least Two Symptoms Resolved. The patients who were classified as a failure but had at least two symptoms resolved were evaluated more closely. Three of the failed patients each had a persistence or progression of radiographic abnormalities (a pre-specified "failure" definition) at TOC. Patient 1 improved over time and symptoms resolved from Days 3–5, but the patient had persistence or progression of radiographic abnormalities at the TOC visit. Patient 2 had sporadic improvement and a normal chest radiograph at TOC. Patient 3 had chest pain and cough that were resolved at Day 5 but came

back at the TOC; this patient also had persistence or progression of radiographic abnormalities. These discrepancies should not be over-interpreted and could have been due to worsening of a baseline symptom or the presence of symptoms outside those recorded. The final patient showed resolution according both to the study definition on study Days 3–5 and based on the symptom data at TOC follow-up; there was no clear reason why this person failed in the disposition data set. However, this patient had a medley of other problems and was taking several concomitant medications including some potentially effective antibiotics. As for the first three patients, other symptoms could have worsened or been present at baseline and resulted in the failure classification.

Conclusions From Review of the Ceftriaxone Dataset

- The data are limited by recording of only present/absent for each symptom and do not correspond to the study protocol's definitions for improvement.
- The number of patients with symptoms of interest at baseline is similar to what was observed previously: 98% of patients had two or more symptoms at baseline.
- Symptoms at baseline were similar for patients who were classified as cure or failure.
- With the caveats noted above regarding the meaning of the TOC assessment, one-symptom resolution did not correlate well with an assessment at the TOC visit. On the other hand, two-symptom resolution had a broad, general agreement with the TOC assessment and with the analysis of the levofloxacin-tigecycline dataset.
- Three of four failures (75%) who did show resolution of two or more symptoms on Day 5 had persistence or progression of radiographic abnormalities.
- Forty percent of patients who were an investigator-determined cure at TOC did not have two or more symptoms resolved from baseline by Study Day 5. In particular, cough was noted to be a persistent symptom that did not resolve completely with antibiotic therapy during the usual observation period.
- Overall, these findings are consistent with the observation from the tigecycline-levofloxacin data set that improvement of two or more symptoms on approximately Day 4 of therapy (approximately 72h into the course of therapy) is indicative of response to therapy.

2.1.5 Analyses Undertaken During Review of the Ceftaroline Phase 3 CABP Studies

The FDA has recently reviewed two phase 3 non-inferiority trials compared ceftaroline with ceftriaxone in the treatment of adults with CABP and on the basis approved ceftaroline for this indication. Enrolled subjects had mean age of 61 years with 62% of the subjects in PORT category III and 38% in PORT category IV.

As noted in the FDA-approved prescribing information, "To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterial agents may be supported by historical evidence. The analysis endpoint required subjects to meet signs and symptoms criteria at Day 4 of therapy: A responder had to both (a) be in stable condition according to consensus treatment guidelines of the Infectious Diseases Society of America and American Thoracic Society, based on temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status (Mandell, Wunderink et al. 2007); (b)

show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms."

The response rates at study Day 4 for microbiologically evaluable patients were 69.6% and 69.0% for ceftaroline and 58.3 and 61.4% for ceftriaxone for trials 1 and 2, respectively.

The FDA reviewers also suggested that knowing whether the clinician was assessing stability based on the above-noted definition at that earlier time point could help in the evaluation of efficacy as a measure in addition to symptoms and evaluated separately (not as a composite outcome measure). FDA evaluated the literature that IDSA/ATS has published on the criteria for establishing stability. These objective criteria for stability (body temperature ≤ 37.8 °C, pulse $\leq$ 100 beats per minute, respiratory rate ≤ 24 breaths per minute, stable blood pressure ≥ 90 mm Hg, oxygen saturation $\geq 90\%$, and normal mental status) have been suggested as a means to help clinicians understand when it is appropriate to discharge a patient from the hospital. Although only one element of this definition is directly tied to how a patient feels or functions (normal mental status), the FDA view parallels the practical clinical sense that these measurements are directly tied to the historical data on response and can serve to support a non-inferiority margin. The quantitative relationship between biomarkers and symptoms is an area that needs further research, as correlations between biomarkers and outcomes of how patients feel, function and survive may represent a useful starting point but are insufficient to evaluate and qualify biomarkers as outcome measures.

As also stated in the FDA-approved prescribing information, FDA concluded that the historical data available at the time of this drug's review were insufficient to establish the magnitude of the drug effect for antibacterial drugs using clinical response at the TOC time point. However, the FDA review team determined that the product label should provide a full description of the entire course of treatment for CABP. The protocol-specified analyses in the CABP trials included the clinical cure rate at the test of cure (TOC) visit (8–15 days after treatment ended).

Conclusions From Review of the Ceftaroline US FDA CABP Registration Dataset

- A recent drug registration has been based on a response definition based on (a) achieving clinical stability based on temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status (Mandell, Wunderink et al. 2007) and (b) showing improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms.
- In this analysis, improvement at Day 4 of symptoms along with stabilization of signs over the previous 24 hours was thought to be a reasonable choice of time for assessing the endpoint. But, Day 3 or 5 could perhaps also be used pending further analysis.
- The use of the early endpoint presumes that there is a later secondary outcome measure that captures overall outcome; relevant measurements such as temperature, respiratory rate, blood pressure, and oxygenation should be approached as supportive secondary measurements, and the IDSA/ATS guidelines provide a good reference for clinical stability based on vital sign measurements.

2.1.6 Data Not Yet Available and Needed for Project Team's Final Recommendations

(Please also refer to Section 2.2)

As summarized below, these analyses demonstrate the potential value of an early endpoint measure that is based on the symptoms of cough, chest pain, dyspnea, and sputum production. As demonstrated by the analysis of the ceftaroline registrational dataset, resolution of these symptoms in combination with demonstration of physiological stability (the temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status stability parameters discussed above) offers an endpoint that offers advantages of a strong link to historical evidence of a substantial antibiotic treatment effect size relative to placebo and an objective approach to documenting improvement of the patient symptoms.

Although there are gaps in our knowledge regarding such an endpoint, the consensus opinion of the Project Team is that an endpoint based on these ideas could be used now to enable trials to proceed in this area. Additional work is needed to refine our understanding of such an endpoint, but there is a critical need for a bridge period with the use of interim efficacy endpoints. Thus, the ideas in this document are recommended for immediate use.

For the future, however, areas that require further clarification are

- Specific enrollment criteria
- Identification of alternative endpoints, including those that might be suitable for assessing response in patients with greater or lesser degrees of baseline severity of illness and symptoms. For example, critically ill patients may not be able to provide direct reporting on their symptoms.
- Are symptoms other than the four identified from these data relevant? Can the simple scoring scheme of Absent, Mild, Moderate, and Severe be better defined or made more robust?
- An approach to the important measures of clinical stability based on the temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status stability parameters discussed above needs to be developed. Principally composed of physiological biomarkers, the FDA's approach to the ceftaroline dataset evaluated these relevant measures as elements of a composite outcome measure in that therapy was required to demonstrate an effect on symptoms as well as these related measures. Is this the most informative approach? The data that group evaluated showed that this would lower overall success rates as measured in current trials.
- Selection of the optimum time(s) for endpoint evaluation.
- Are alternative endpoint rules needed for drugs of other classes? The Project Team recognized that the data were derived based on drugs from a limited number of classes (beta-lactams, fluoroquinolones, and tetracyclines), that the pace of response might vary among drug classes, and that the endpoint rule might need to be reconsidered in the future as additional data for other drug classes become available.

2.1.7 Conclusions

1) There is strong support that an early clinical endpoint (e.g. Day 4, see below) of symptom improvement gives relevant data on how a patient feels and functions and provides evidence of a strong treatment effect size for antibiotics via its link to less well-defined assessments of symptom improvement in historical studies.

2) The four symptoms identified in the review to date (cough, pleuritic chest pain, dyspnea, and sputum production scored as Absent, Mild, Moderate, and Severe) are biologically relevant to the disease and are recommended. It may be possible to utilize other symptoms, but including others would require a new definition for what is considered a success and new datasets for analysis. Evaluations of whether all relevant symptoms are included in current definitions should be a focus for future research.

3) The overall measure proposed at present by the Project Team builds on these three elements:

   a) A one-point improvement in at least two symptoms and

   b) No worsening of any other symptoms with

   c) The assessment made on study Day[3] 4.

4) Assessment at Days 3 and/or 5 is also plausible, but measures at these times were more often discordant with overall clinical response in the available dataset. This finding is not robust as the differences may have been in part due to different numbers of observations on each Day. The extent of discordance is also dependent upon the response definition. Thus, Day 4 should be viewed as reasonable choice but also one that could be challenged by future data.

5) Of note, the proposed early clinical endpoint does not consider other interim events. Subjects who die before the Day 4 endpoint would lack data showing improvement and would of course be judged as Non-Responders. However, subjects who required a change in therapy due to a complication or adverse event might be judged at the early response timepoint as a Responder if initiation of alternative therapy produced an adequate response by Day 4. Although one might expect someone who received alternative therapy to be scored as a Non-Responder, the Project Team proposes scoring the early response measure based solely on clinical response. As the Project Team expects such discordant situations to be uncommon, the numerical impact on the early response endpoint should be insignificant. This type of event should be identified in secondary analyses.

6) There are important alternative viewpoints on the use of the proposed endpoint. In brief, the concerns focus on the limited data to support the new endpoint, the early endpoint's inability to capture the entire treatment course, and the potential challenge of using this endpoint in

[3] Throughout this document, Study Day 1 corresponds to the day of initiation of study therapy. An observation on Study Day 2 (usually the next calendar day) would be taken approximately 24h after initiation of therapy, an observation on Study Day 3 would be taken approximately 48h after therapy initiation, Study Day 4 would be approximately 72h after therapy initiation, and Study Day 5 would be approximately 120h after therapy initiation. The datasets discussed in this paper did not rigidly define specific time windows but rather appear to have followed a largely calendar-day based convention.

parallel with other endpoints as part of a global development program. These are discussed in detail in Section 3.2.

2.2 Phase 2: Qualitative Research Phase

The review of the available data by the Project Team revealed several research gaps in both defining all the relevant symptoms of importance to patients and in evaluating the reliability of measurements of patient symptoms. While it is critical to develop interim recommendations to allow drug development to proceed, it is equally critical to perform research to evaluate the validity and reliability of these recommendations or to improve upon them if needed. This research should be performed in as a timely a fashion as possible. It is planned that one or more research firms will be selected through a formal RFP process to complete a qualitative research phase of instrument development that would be based on both literature searches and patient interviews. This work might lead to improved outcome measures for future clinical trials in CABP.

The proposed studies will be conducted by a group of researchers highly experienced in the field of infectious disease, and will be guided by a Project Team that includes academic clinicians, drug development personnel from pharmaceutical companies, and representatives from the NIH, and the FDA.

Results from the retrospective clinical trial analyses and qualitative research studies will be used as input to designing prospective clinical studies to be conducted as part of a potential Phase 3, which would be proposed as a separate Biomarkers Consortium project and be focused on the design and conduct of one or more clinical studies to further test and validate specific endpoints and measurement approaches. While a standalone study cannot be ruled out, it is expected that these later studies will be able to be coordinated as companion studies to current trials being conducted by NIAID (National Institutes of Allergy and Infectious Diseases) or industry.

3 Interim Recommendations

3.1 Description of an Early Endpoint

1) Study design
    a) Most studies comparing one active agent with another would be of an non-inferiority design due to ethical and feasibility issues.
    b) Superiority trials are difficult to implement for serious or life-threatening infections unless there are no other active agents available. The one exception is add-on studies in which a second active agent is added to the base regimen, but achieving a superior effect over a fully dosed and active base regimen would be unlikely in setting where there is already effective therapy.
    c) Dose-response and placebo-controlled superiority study designs could be used in selected mild infections. Specific situations such as randomized dose-response trials and combination therapy trials do offer the tantalizing possibility of providing data on which to base the design of future non-inferiority trials.

d) However, an additional limitation is that the subjects who can be enrolled may have such limited and mild infection that the results cannot be generalized beyond the context of use in the given clinical trial to other patient groups with more severe forms of the illness.
e) Note that novel well-defined, reliable, and clinically meaningful endpoints can be used in superiority trials since there is no requirement for evidence of treatment effect from prior studies to evaluate assay sensitivity in the setting of superiority trials.

2) Endpoints
   a) Early assessment at Study Day 4, approximately 72h[4] after baseline measurement at time of randomization and treatment initiation, supports treatment effect by demonstration of
      i) A one-point improvement in at least two symptoms and
      ii) No worsening of any other symptoms
      iii) Where symptoms are Cough, Dyspnea, Pleuritic Chest Pain, and Sputum Production
      iv) And symptoms are scored as Absent (or none), Mild, Moderate, and or Severe.
   b) Later assessment at a fixed time point after initiation of therapy
      i) The Project Team did not debate the precise requirements for a later assessment endpoint and identified this as a topic for future research. Typical elements from prior studies would include
         (1) Survival,
         (2) Improvement (or resolution) of the clinical signs that are part of the early assessment endpoint,
         (3) Lack of a requirement for modification of therapy, and
         (4) Lack of adverse events leading to discontinuation of therapy.
      ii) The late assessment might or might not include a requirement to have been judged a Responder at the early endpoint (see the discussion on Alternative Viewpoints (Section 3.2).
      iii) To address the need for international harmonization of clinical trial design, the late endpoint could in fact be two time points; one at the end of therapy (EOT) and the other at an off-therapy (i.e., TOC) time point.
      iv) The best time(s) for the late endpoint(s) should be determined depending on the maximum length of treatment, the pharmacokinetic (PK)/pharmacodynamic characteristics of the drug, and the characteristics of the comparator agent.
      v) Assessments should be made at a fixed time point relative to the baseline measurement and study initiation that is the same across patients.
      vi) Collection of sufficient PK data to estimate individual subject drug exposure would allow for more complete exposure-response analyses for both early and late endpoints.
   c) Absence of elevated body temperature is not recommended as part of the early endpoint since it may be confounded by antipyretic therapy. Although persistent fever is occasionally due to a non-infectious cause such as drug-related fever, overall successful response without resolution of elevated body temperature would be unusual and its

[4] Throughout this document, Study Day 1 corresponds to the day of initiation of study therapy. An observation on Study Day 2 (usually the next calendar day) would be taken approximately 24h after initiation of therapy, an observation on Study Day 3 would be taken approximately 48h after therapy initiation, Study Day 4 would be approximately 72h after therapy initiation, and Study Day 5 would be approximately 120h after therapy initiation. The datasets discussed in this paper did not rigidly define specific time windows but rather appear to have followed a largely calendar-day based convention.

resolution is of interest to patients and physicians. It should thus be included as a sensitivity analysis and/or as part of a late assessment endpoint.

d) Parallel with the just-discussed issue of the resolution of elevated body temperature, improvement in the important measures of physiological clinical stability (e.g., the parameters suggested by the IDSA/ATS guidelines (Mandell, Wunderink et al. 2007)) would be expected but is not specifically part of the symptom-based endpoint described in this work. A conclusion of response based on symptoms without simultaneous achievement of such clinical stability would be unusual and would suggest an inter-current second process.

3) Study enrollment criteria
   a) This issue was outside of the scope of this project and was not discussed in detail by the Project Team. Diagnostic criteria similar to those in the March 2009 FDA Draft CABP guidance (Food and Drug Administration 2009, March) were presumed during Project Team discussions with key elements of standard clinical symptoms and PORT Risk Class of III or more. The issue of exclusion due to prior receipt of effective antibiotics was not analyzed by the Project Team. Likewise, the sample size challenge created by limiting the primary analysis to the microbiologically proven subset of patients was not discussed by the Project Team.
   b) As the proposed response endpoint rule requires improvement of at least one point for two symptoms, a minimum of two symptoms are required for study entry.

4) Although outside of the scope of this project and not discussed in detail by the Project Team, it was noted that late response should be assessed at fixed time points post-randomization or initiation of therapy to ensure a consistent duration of assessment time for successes and failures.

5) Proposed non-inferiority margin if applicable: This topic was not specifically discussed by the Project Team.

6) Sample size considerations: This topic was not specifically discussed by the Project Team.

7) Opportunities for harmonization globally
   a) See discussion above regarding choice of primary endpoint. These data could be presented to regulatory authorities in other countries for their evaluation. FDA members of the review group have offered to share these analyses with other regulatory agencies

8) Studies/ data needed to advance to final recommendations and timeframe for accomplishing same: Phase 2 data as described above.

3.2 Alternative Viewpoints, Issues, Limitations, and Areas for Future Work

There are alternative viewpoints within the Project Team regarding the conclusion that the primary measure should be taken at Day 4 of therapy. Although there was agreement among team members that the early measurement provided important information, some concerns were raised and should also be addressed in future research:

a) ***These endpoints rely in part on data from a very different medical era.*** Although biologically plausible, the specific proposal developed for elements of the proposed early endpoint is based on a small number of datasets, some of which are very old and which represent medical experience during an era that provided very different levels of supportive care.

b) ***Currently available agents are active for life-threatening infections such as CABP.*** Although there are demonstrated instances of detection of differences in efficacy or safety among agents for life-threatening infections as well as instances of detection of ineffective agents that were not subsequently registered for the given indication (e.g., daptomycin for pneumonia), currently available agents approved using traditional late assessment TOC endpoints are suitable to use as comparators in future trials (Spellberg 2011). As discussed below, some justification for this is that traditional late assessment TOC endpoints have always implicitly included a requirement for an early response, albeit not necessarily in a formal manner.

c) ***Recent pharmacometric analyses show a correlation between drug exposure and TOC endpoints***. A recent presented observation (Ambrose 2011; European Medicines Agency 2011) is that pharmacometric exposure-response analyses demonstrate a correlation of drug exposure with traditional clinical and microbiological endpoints.
    i) Arguments in favor of the plausibility of these correlations include:
        (1) The demonstrated relationships indicate that contemporary clinical endpoints (e.g. success or failure at the TOC) capture a measure of drug effect.
        (2) These analyses produce estimates of treatment effect relative to placebo which are similar to estimates derived from other sources but that are derived using current data from modern studies and thereby could negate concerns of meeting the constancy assumption.
        (3) The consistency of these observations (similar results can be shown for across both multiple indications [HAP, VAP, CAP, ABSSSI, and ABECB] and multiple antibiotic classes), the biological plausibility of the observations (drug effect should decline as exposure declines), the retention of the correlations when the analysis is controlled for age, severity of illness, or co-morbid disease, and the lack of an hypothesis regarding a host immune factor that would correspondingly alter drug exposure lend support to the need to consider carefully this approach.
        (4) In particular, this approach offers the possibility of validating non-inferiority margins using modern trial designs and modern endpoints. Moreover, pharmacometric exposure-response analyses offer the possibility of linking early and contemporary late clinical endpoints.

ii) This approach, however, can also be critiqued:
(1) Although these analyses are useful for identifying prognostic factors and generating hypotheses regarding plausible doses and schedules to be studied in properly conducted randomized trials, attempts at causal inferences from such analyses are biased due to confounding between treatment effects and prognostic patient characteristics.
(2) Specifically, it is not sufficient that exposure or organisms may be randomly assigned, since host factors are not randomly assigned and these latter factors cannot be adequately accounted for by matching. People with differing concentrations or minimum inhibitory concentrations can differ on other factors that affect outcome, like age, severity of illness, co-morbid disease, or many other covariates, and most of these are unidentified or unrecorded. Inherent differences in such patient characteristics are sufficiently influential to lead to substantial differences in concentrations; therefore it is likely that these inherent differences are also meaningfully predictive of the outcome measures.
(3) The consistency of results across settings may thus be explained by consistency of this same bias across those settings.

d) ***Early time points are already part of the traditional late assessment TOC outcome.*** An early measure of response is included in all clinical trials, but the timing and formality of this evaluation may differ from trial to trial and there is not a systematic requirement for investigators to make a final assessment at this time point. If improvement is not apparent at Day 3 or 4, the patient is generally withdrawn from study medication and the response defined as a failure for effectiveness analyses. These outcomes are carried forward for purposes of analyses at later time points. In some trials, this early assessment has been entirely informal and is captured only by noting whether the physician and patient continued the randomized therapy. In other trials, a formal recording a decision to continue has been taken. A systematic analysis of early time points with clear definitions of outcomes would help clarify the analysis of trial results. A great strength of the work presented here is that it provides a basis for documenting the reasoning that goes into the decision to continue or discontinue therapy at an early time point. Early and later time point assessments are not mutually exclusive and can both be measured in the setting of clinical trials.

e) ***Later endpoints provide a key overall perspective.*** While all team members agreed that early measurement provided important information on drug effects, some members of the Project Team believed that the primary outcome measure should be assessed at the EOT or beyond. The suggestion to use a later primary endpoint included these concerns:
i) Overall clinical cure at a late time point following EOT is important to evaluate durability of response and should be noted in the product labeling. Given that this measure thus takes on the role of being the principal measure that is relevant to the use of a drug, it could be argued that this measure best meets the ICH E9 (Section 2.2.2) test that: "The primary variable ('target' variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial."
ii) Use of the early endpoint as the primary study endpoint has not to date been specifically endorsed by other regulatory agencies. Global trial design harmonization is an important

goal and the full implications of the use of dual statistical analysis plans have yet to be understood by the community.

iii) As an example of a specific alternative approach, an overall endpoint which required both success at the early endpoint based on the rules proposed below (see Section 3) AND success at a later overall time such as at a typical TOC time point (preferably assessed using a direct measure of how a patient feels, functions or survives, lack of requirement for other therapy, lack of complications, etc.) could be considered to (i) incorporate the known effect size, (ii) capture the entire pattern of response, and (iii) address the concern that success rates inevitably rise over time such that even placebo-treated patients recover (or have died). If the effect size relative to placebo is sufficiently large for the early endpoint, the small number of patients who subsequently convert from success at the early endpoint to failure at the late endpoint (e.g., <5% in the tigecycline analysis) still supports a large effect size (**Figure 3**). This idea follows naturally from the critique of the traditional TOC endpoint discussed in Section 1.1 of this document and mimics the standard clinical (and clinical trial) practice of using a patient's early response to determine if therapy is adequate and suggests a connection between the demonstration of the ability of standard trial designs to detect inadequate drugs or exposures (see above). Combining the strength of a well-defined and objective early measure with the clinical relevance of the overall endpoint offers a potentially useful alternate option to the primary assessment at the time of the early endpoint. For example, such an approach might support international harmonization.

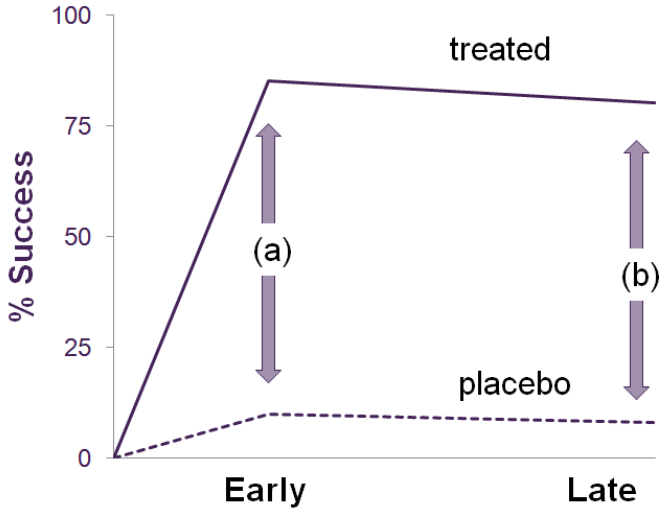


Figure 3. Estimating a late treatment effect using the estimate for an early treatment effect. If there is a large early effect AND if success at the late time (e.g., a typical TOC timepoint) requires early success, then a large treatment effect will still be present. As an example, the treatment effect at early times (a) for CABP is > 70% (see early sections of this document for data from Osler 1910, Bullowa 1937, Meakins 1939). In the data discussed by the working group, rates of discordance between the early endpoint and a late (TOC) clinical endpoint were < 5% (Section 2.1.3).

f) ***Time to response may provide useful insights.*** Since clinicians often choose to change therapy in the absences of response within two or three days, the early time point must have some value in addition to later time points evaluating durability of response or other variables such as relapse or adverse events. Time to response may also be an important measure but

not one for which at present there are data to pose a hypothesis for a non-inferiority trial. This is an approach that could be considered as additional data become available for analysis.

4 Conclusions

In the process outlined above various stakeholders including members from academia, industry and government agencies proposed interim, bridging outcome measures for registrational trials in the CABP indication.

These interim outcome measures are based on an evidence-based analysis of the historical literature that showed a treatment effect of antimicrobials in CABP based on symptom improvement at Day 4 after the first dose of study drug. While other outcome measures are relevant, there is insufficient evidence at present to base future non-inferiority trials solely on those outcomes. These outcomes could be studied by testing superiority hypotheses in future studies or possibly be based on new data such as the insights coming from recently presented pharmacometric exposure-response analyses.

The proposed early time point shows a substantial treatment effect for antimicrobials (approximately 30%; Section 2.1.2 above), allowing assessment of the non-inferiority of active agents at this time point. This large treatment effect (M1) provides a solid justification for selection of an M2 on the basis of clinical reasoning.

These interim outcome measures allows registrational studies to proceed while the Project Team plans future qualitative and quantitative research studies to evaluate the relationship between outcome measures in CABP and the operational characteristics of various measurement methods and time points in assessing outcomes in CABP. These future studies are critical in addressing knowledge gaps related to designing trials in CABP.

5 Supplemental Data

5.1 The Course of Untreated Pneumonia

1) The description provided by Osler in 1910 of the presentation of untreated pneumonia is particularly detailed (Osler 1910)
   a) When seen on the second or third day, the picture in typical pneumonia is more distinctive than any other acute disease.
   b) The patient lies flat in bed, often on the affected side; the face is flushed, particularly one or both cheeks; the breathing is hurried, accompanied often with a short expiratory grunt; the alae nasi dilate with each inspiration; … the eyes are bright; the expression anxious; and there is a frequent short cough which makes the patient wince and hold his side.
   c) The expectoration is blood-tinged and extremely tenacious.
   d) The temperature may be 104° or 105°.
   e) …
   f) After persisting for seven to ten days, the crisis occurs, and with a fall in the temperature the patient passes from the condition of extreme distress and anxiety to one of comparative comfort.

2) Osler provides these supplemental details in other parts of his review:
   a) Pain (pg. 174): "There is early a sharp, agonizing pain, generally referred to the region of the nipple or lower axilla on the affected side, and much aggravated on deep inspiration and coughing. It is absent in central pneumonia and much less frequent in apex pneumonia."
   b) Dyspnea (pg. 174): "Dyspnea is an almost constant feature. Even early in the disease the respirations may be 30 in the minute, and on the 2nd or 3rd day between 40 and 50. The movements are shallow, evidently restrained, and if the patient is asked to draw a deep breath he cries out with the pain."
   c) Cough (pg. 175): "This usually comes on with the pain in the side, and at first is dry, hard, without any expectoration. Later it becomes very characteristic – frequent, short, restrained, and associated with great pain in the side. In old persons, in drunkards, in the terminal pneumonias, and sometimes in young children, there may be no cough. After the crisis, the cough usually becomes much easier…"
   d) Sputum (pg. 174): "At first it may be mucoid, but usually after 24h it comes blood-tinged, viscid, and very tenacious. … in 100 cases in my clinic, in 16 there was little or no sputum, in 32 it was typically rusty, in 33 blood-streaked, in 3 cases very bloody. After the crisis the quantity is variable, abundant in some cases, absent in others"

3) Similar to Osler, Bullowa's 1937 description reinforces the sense of substantial morbidity but also gives insight into a steady deterioration during the early course of disease:
   a) "After four or five days, …
      i) …the patient who has become irritable and peevish, beings to "see things", is obstreperous, suspicious, and thinks he can take care of his own affairs. Under hypnotics, he may doze or become lethargic.

ii) By this time, the pain in his side has abated but the patient is distended and slumped in bed.
iii) He is cyanosed and breathes rapidly with effort.
iv) His pulse becomes rapid (120 or more), he refuses food and his weakness and emaciation are progressively severe
v) He becomes incontinent of stool and urine.

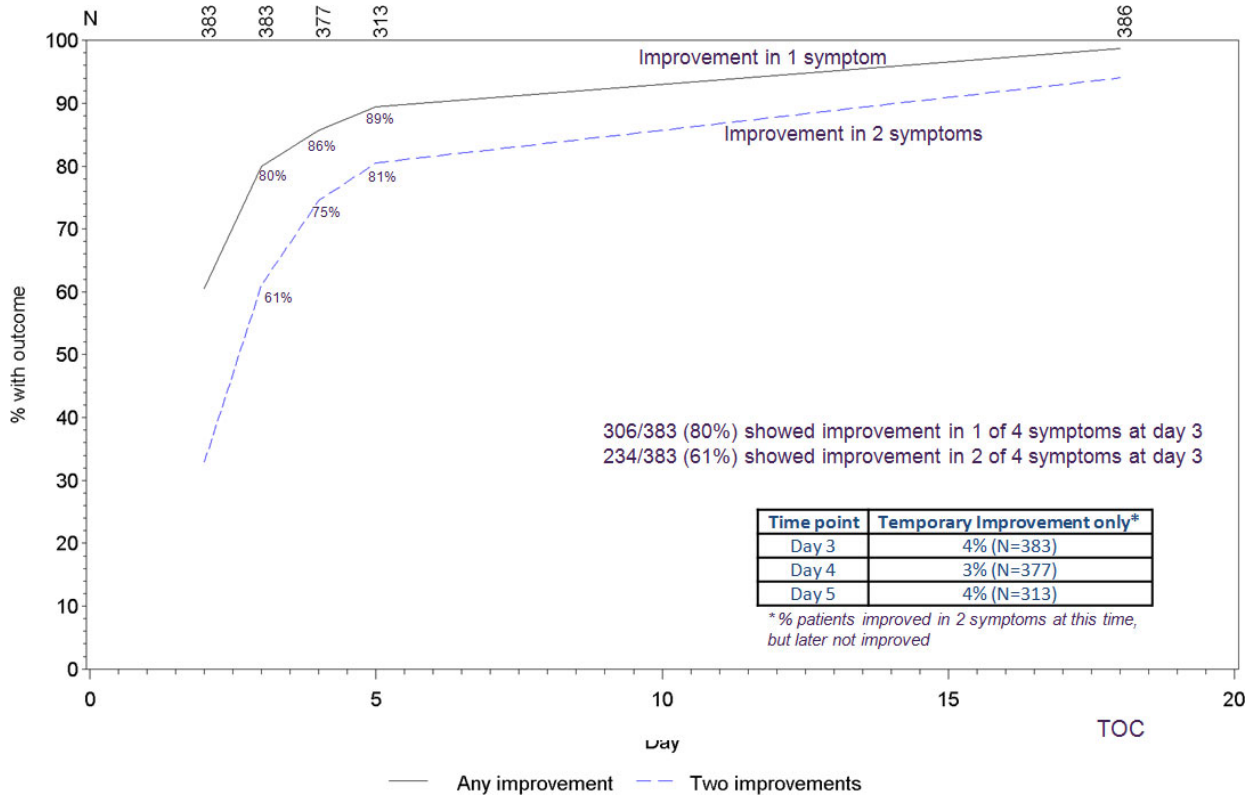
b) After eight or nine days, …
i) … the temperature falls following a drenching sweat. The patient then convalesces over several weeks, unless, after a few days there is an exacerbation of fever with the onset of a suppurative complication."

5.2 Supplemental Details from the Tigecycline-Levofloxacin CABP Dataset

Table 6: Frequency of baseline symptoms in the patient cohort

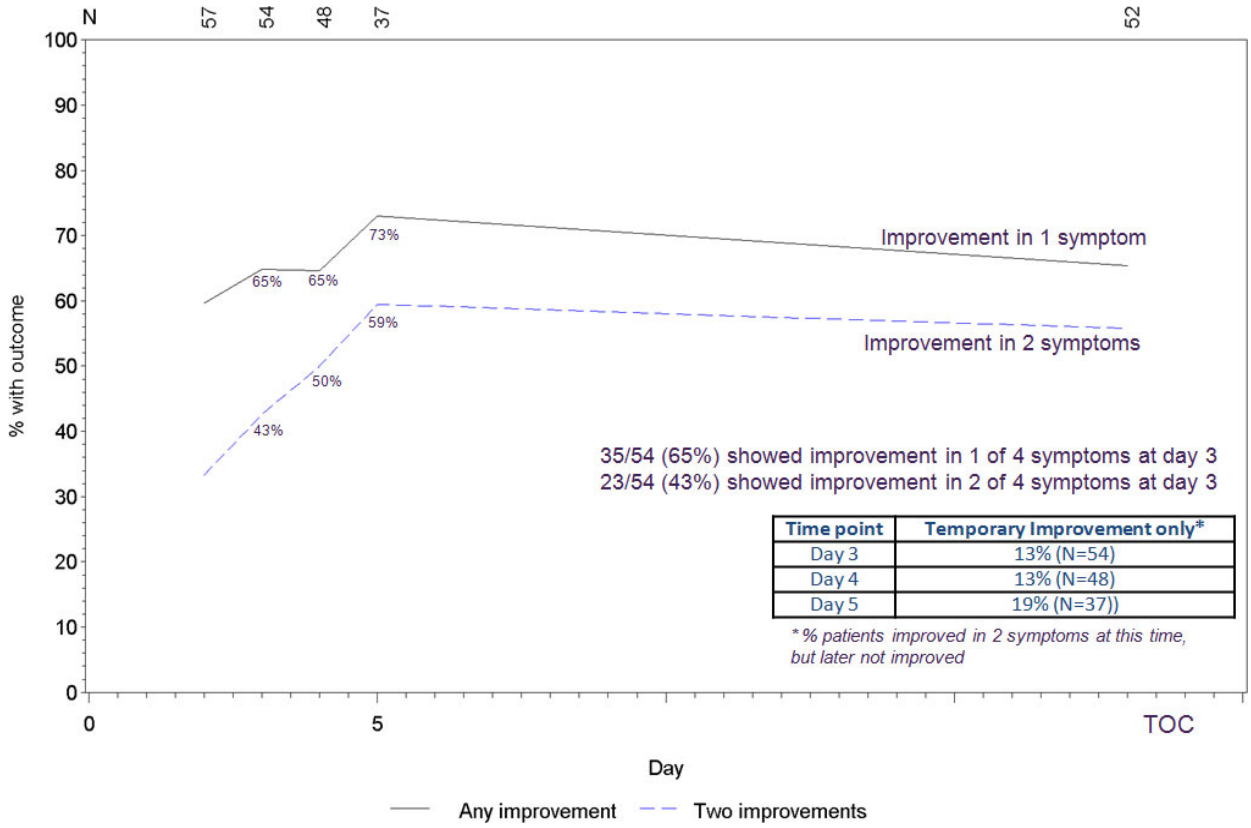
Number of symptoms for which the score at baseline was Mild, Moderate, or Severe	TOC clinical response		Total
	Cure	Failure	
1	15	4	19 (4%)
2	56	9	65 (14%)
3	136	21	157 (34%)
4	179	37	216 (47%)
Total	386	71	457

Figure 4. Improvement in CAP symptoms in patients judged Cured at the TOC visit



Temporary improvement rates use the total number of cures/total number of failures at TOC

Figure 5: Improvement in CAP symptoms in patients judged Failed at the TOC visit



Temporary improvement rates use the total number of cures/total number of failures at TOC

6 Project Team Members

The conclusions described within this document represent the work of the FNIH Biomarkers Consortium Project "Developing Endpoints for Clinical Trials of Drugs for Treatment of Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia (Phases 1 and 2)".

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APPENDIX 2

DISCUSSION TOPICS ON ENDPOINTS AND CLINICAL TRIAL DESIGN FOR CABP

1. Overview of Efficacy Considerations

Treatment for CABP involves the administration of antibacterial drugs for approximately 1 to 2 weeks. The goal of CABP clinical trials should be to demonstrate an effect of antibacterial therapy on improvements in clinical responses during treatment and sustained clinical responses after the completion of antibacterial drug treatment. CABP is caused by bacterial pathogens such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, *M. catarrhalis,* or *L. pneumophila*.[1]

Active-controlled clinical trials in CABP can be designed to show superiority or noninferiority. For the endpoints used in noninferiority clinical trial design, having a reliable estimate of the quantitative treatment effect of the active-control drug is essential. One endpoint is all-cause mortality at 28 days for which a reliable estimate of the quantitative treatment effect can be established. We recognize that a trial designed for using 28-day all-cause mortality as a primary endpoint may not be practicable to conduct because mortality rates in recently-conducted CABP trials are low (e.g., mortality rates of approximately 2% or less). Another efficacy endpoint is based on improvements in clinical symptoms (see section 5, Efficacy Endpoints). Evidence in the historical literature supports a treatment effect based on the clinical assessment of patients earlier during the course of therapy at day 3 to day 5 of therapy (see section 8 for the justification for noninferiority margin).

Essential secondary endpoints include the assessment of clinical signs during therapy (e.g., vital signs, arterial oxygenation), and the assessment of complete resolution of signs and symptoms at the end of study therapy and at 10 to 14 days after completion of therapy. These additional secondary endpoint assessments are important assessments in determining response to antibacterial drug treatment and resolution of disease, and whether relapses are occurring after therapy has been completed. Mortality will always be evaluated as an important safety endpoint in any trial.

Additional development work is necessary for an endpoint of improvement in symptoms at day 3 to 5, for example an evaluation within phase 2 trials. This work in phase 2 may help

[1] These bacterial pathogens for CABP are most often associated with patients that have a greater severity of illness where there is a greater treatment effect to support the noninferiority clinical trial design. We recognize that other bacteria cause CABP, such as *M. pneumoniae* and *C. pneumoniae* but are often associated with patients who have a lesser severity of illness. For any other particular organism as a pathogen in CABP, additional data should be provided to substantiate the claim as a bacterial pathogen in CABP.

in the development of techniques to assess the endpoint and provide information to assess how the endpoint performs (e.g., success rate in the condition being studied, an important consideration for sample size calculations for phase 3 trials).

We encourage the development of appropriate instruments to assess endpoints in clinical trials. For example, symptoms of pneumonia that can be best measured from the patient perspective should be measured with a patient-reported outcome (PRO) instrument. Development of a new PRO instrument or Drug Development Tool (DDT) should begin well in advance of phase 3 clinical trials. A new efficacy endpoint such as a PRO or DDT to be used in a noninferiority trial should capture clinical symptoms that are attributable to CABP and symptoms that also reflect the observations and stability of clinical signs (e.g., chills/rigors/"feverishness" as the symptom manifestation of an elevated body temperature). A new efficacy endpoint early in the course of therapy for CABP (i.e., day 3 to day 5) for noninferiority trial designs should include the improvement in clinical symptoms of chest pain, frequency or severity of cough, amount of sputum production, difficulty breathing, chills/rigors/"feverishness", functional abilities such as eating or walking, or other improvements in clinical symptoms important to the patient at day 3 to day 5 after initiation of clinical trial drugs. Given that patients in CABP trials may be severely ill, the PRO or DDT should be adequately designed to account for these types of patients.

While a new efficacy endpoint is in development and has not yet been qualified for use, an interim endpoint can be used that is based on improvement of symptoms attributable to CABP at day 3 to day 5 after initiation of clinical trial drugs, which should include at a minimum the improvement clinical symptoms of chest pain, frequency or severity of cough, amount of sputum production, and difficulty breathing. We also recommend that the interim endpoint include the improvement in symptoms of chills/rigors/"feverishness", improvement in functional abilities such as eating or walking, or other improvements in clinical symptoms important to the patient. In addition, the protocol for a clinical trial should describe how patients will characterize their symptoms as "absent", "mild", "moderate", or "severe".

For drugs that have only an IV formulation available, we recommend that clinical trials be conducted with the IV formulation alone, without switching to an oral antibacterial drug, to allow for assessment of both the efficacy and safety of the investigational drug. However, if a complete course of therapy with an IV formulation is not practical (e.g., because of considerations such as patient convenience and risks associated with an indwelling venous catheter) a study design may be considered that incorporates a switch from the investigational IV drug to an FDA-approved oral antibacterial drug. In the setting of a study design that includes switching to an FDA approved oral antibacterial drug, the endpoint evaluated at day 3 to day 5 (e.g., the interim endpoint of improvement in clinical symptoms) should be completed before switching to oral therapy. Assessment of the primary endpoint at day 3 to 5 prior to switching to an FDA approved oral antibacterial drug should ensure that the evaluation of efficacy reflects the effects of the investigational IV drug. The overall duration of antibacterial drug therapy (i.e., days of IV therapy plus days of oral drug therapy) when switching to an FDA-approved oral antibacterial drug should not exceed the recommended duration of therapy for either the IV investigational drug or the

FDA approved oral antibacterial drug (e.g., 5 days of IV investigational drug followed by 2 days of oral FDA-approved drug for a total of 7 days of therapy for CABP). Avoiding an unnecessarily long course of oral switch therapy may allow for greater clarity that the IV investigational drug is contributing to overall efficacy on secondary endpoints at the end of treatment and 10-14 days after completion of treatment.

For drugs that have both an IV and oral formulation, appropriate criteria that allow for IV to oral switch should be specified in the protocol and listed on the case report form. The pharmacokinetics of the oral formulation should have been adequately evaluated to ensure comparable exposure and to determine an appropriate dosing regimen. If practice patterns allow, it may be appropriate to enroll hospitalized CABP patients in oral antibacterial trials.

2. General Safety Considerations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. All patients should be evaluated for safety at the time of each visit or assessment, regardless of whether the test drug has been discontinued. While serious and unexpected adverse events and follow up information about the events are required to be reported (21 CFR 312.32 (c)(1)(i)(A) and 21 CFR 312.32 (d)(1) and (2)), we recommend that in general all adverse events should be followed until resolution, even if time on study has been completed. We recommend that a pre-approval safety database contain approximately 1,000 to 1,500 patients at the dose and duration of therapy for treatment of CABP.

A sufficient number of patients, including patients older than 65 years, should be studied at the dose and duration proposed for use to draw appropriate conclusions regarding drug safety. Safety evaluations and assessments should take into consideration the patient populations that are likely to be treated for CABP. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be needed based on the nonclinical and clinical profile of the specific drug under investigation. Longer term assessment of adverse events after discontinuation or completion of the antimicrobial should be considered, depending on the specific drug's potential for long-term or delayed adverse effects.

3. Clinical Trial Design

CABP trials should be randomized, double-blind, and active-controlled using a noninferiority or superiority design. Placebo-controlled trials are not appropriate for this indication. The trial population should include patients with CABP. For noninferiority trials, an analysis of the pooled micro-ITT population should be performed on patients with a microbiologic diagnosis. For superiority trials, we recommend efforts to document bacteriologic etiology in at least 25% of the patient population.

Clinical, radiographic, and microbiologic entry criteria

The diagnosis of CABP should be based on the following clinical, radiographic, and microbiologic criteria.

Clinical criteria
As part of the clinical picture of CABP, a patient should have at least 2 of the following clinical symptoms:

- Difficulty breathing (e.g., shortness of breath)
- Cough
- Production of purulent sputum from respiratory secretions (i.e., cough productive of purulent sputum)
- Chest pain

In addition to having at least 2 clinical symptoms listed above, other clinical symptoms are optional entry criteria and may be evaluated as part of a symptom response endpoint. These symptoms include, but are not limited to, the following:

- Chills/rigors/"feverishness"
- Decreased or no appetite
- New functional limitations in the ability to walk or perform a usual activity of daily living that are associated with CABP

Additional clinical signs are part of the clinical picture of CABP, and a patient should have at least 2 vital sign abnormalities associated with CABP:

-Vital sign abnormalities associated with CABP:

- Fever, e.g., an oral or tympanic temperature greater than 38.0 degrees Celsius (100.4 degrees Fahrenheit); or hypothermia (less than 35 degrees Celsius)[2]
- Hypotension, e.g., systolic blood pressure less than or equal to 90 mmHg
- Tachycardia, e.g., heart rate greater than or equal to 100 beats per minute
- Tachypnea, e.g., respiratory rate greater than or equal to 24 breaths per minute

And patients should have at least one other clinical sign or laboratory finding associated with CABP:

-Clinical signs or laboratory findings associated with CABP

- Hypoxemia with a partial pressure of oxygen less than 60mm Hg by arterial blood gas or oxygen saturation less than 90 percent by pulse oximetry while

[2] Some patients develop hypothermia, especially the elderly and others who have risk factors such as alcoholism, malnutrition, and other comorbid illnesses.

patient is breathing room air (or while breathing baseline supplemental oxygen) thus requiring the acute administration of supplemental oxygen to maintain oxygen saturation within normal parameters

- Clinical findings of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)
- An elevated total white blood cell count or leukopenia, or elevated immature neutrophils (bands)

Because the treatment effect of antibacterial drugs on the all-cause mortality outcome appears to be greater in patients with ages greater than 50 years and in patients with bacteremia, we recommend enrollment of patients who have, at baseline, a greater degree of severity of illness. The enrollment of patients with a greater severity of illness is an important consideration even for the treatment effect on a nonmortality clinical endpoint such as improvement in symptoms at day 3 to day 5. As an example, a clinical severity scoring system may be used as entry criteria (e.g., the Pneumonia Severity Index or Pneumonia Patient Outcomes Research Team (PORT) classification system using a score of III or higher) and stratification (e.g., ensuring that a certain proportion of patients have PORT scores of IV or higher). The criteria that are used to calculate the severity score and determine the risk class for each patient should be included in the case report form and in the datasets.

- **Radiographic criteria.** The chest radiograph should show the presence of new infiltrates in a lobar or multilobar distribution characteristic of bacterial pneumonia. The final full report of the pretreatment (e.g., at the time of enrollment) and subsequent chest radiograph by the radiologist using standard interpretive criteria should be included in the case report form.

- **Microbiologic criteria.** We recommend that patients have cough productive of purulent sputum at the time of enrollment as one of the clinical symptoms for inclusion; this inclusion criterion may help to maximize the numbers of patients with microbiologic confirmation of pneumonia for the primary analysis population. An adequate specimen of respiratory secretions should be obtained in all patients and sent to the laboratory for Gram stain, culture, and in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen. Specimens should be processed according to recognized methods.[3] Microscopic examination of Gram stained smears should be performed. Specimens that have fewer than 10 squamous epithelial cells and more than 25 polymorphonuclear cells per low power field (100X magnification) are considered appropriate for inclusion in evaluation of respiratory culture results. Ten to twenty fields of the Gram stain smear also should be examined at 1000X magnification and the morphology of potential pathogens recorded. The Gram stain should be performed and the specimen plated for culture within 2 hours from the collection time, if the specimen is kept at room temperature. Alternatively, these tests can be performed within 24 hours of collection if the specimen is stored at 2 to 8 degrees Celsius before processing.

[3] American Society for Microbiology, 2011, Manual of Clinical Microbiology, 10th edition.

The specimen of respiratory secretions can be obtained by any of the following means:

- Deep expectoration
- Endotracheal aspiration in intubated patients
- Bronchoscopy with bronchoalveolar lavage or protected-brush sampling

All isolates considered to be possible pathogens should be saved in the event that additional testing of an isolate is needed. For microbiological assessment, the investigator should collect the following information:

- A description of how the sample was obtained, processed, and transported to the laboratory.

- Identification of the bacterial isolate.

- In vitro susceptibility testing of the isolates to both the study drug and other antibacterial drugs that may be used to treat CABP caused by the targeted pathogens. In vitro susceptibility should be performed by using standardized methods unless otherwise justified.[4] Sponsors should describe the exact methodology used for susceptibility testing if a standardized method was not used.

The use of bacterial detection methods other than culture may be used to define the microbiological intent-to-treat (micro-ITT) population (see section 7 Statistical Considerations). Examples of nonculture detection of bacterial pathogens include: 1) use of rapid diagnostic tests for bacterial pathogens (e.g., urinary antigen test for *S. pneumoniae*); and 2) nonculture methods of testing for bacterial pathogens (e.g., serology, polymerase chain reaction).

Use of rapid diagnostic tests may help to enroll a patient population with the disease of interest (CABP). Similarly, increasing the proportion of patients for whom a bacterial etiology is identified could also have implications for sample size calculations for a CABP clinical trial. The clinical trial of an antibacterial drug may also provide an opportunity to contribute to the development/evaluation of a new diagnostic test. Sponsors interested in also using a clinical trial in patients with CABP as a means for the evaluation of a diagnostic test are encouraged to discuss with the appropriate review division in FDA's Center for Devices and Radiological Health (CDRH).

[4] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute.

If the bacterial detection method has not been approved or cleared for use by the FDA's CDRH, the type and amount of data to be submitted for review should be discussed with us before initiation of the trial.

b. Exclusion criteria

Recommended exclusion criteria include the following:

- Aspiration pneumonia
- Hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia
- Receipt of prior effective antibacterial drugs (see section III.B.7., Prior Antibacterial Drug Use)
- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this does not exclude patients who have chronic obstructive pulmonary disease)
- Patients with primary or metastatic lung cancer
- Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis

4. Choice of Comparators, Prior Antibacterial Drug Use and Concomitant Therapy

The active comparator should be an FDA-approved antibacterial drug that is considered standard of care for this indication (e.g., guidelines published by professional societies) at the recommended dosage.

The use of prior antibacterial drugs effective against bacteria that cause CABP should be avoided in a noninferiority trial because such treatments could reduce the difference between treatment arms and allow an incorrect conclusion of noninferiority. However, patients who have received prior antibacterial therapy and who are considered clinical failures can be enrolled provided objective criteria for treatment failure are prespecified in the protocol and documented on the case report form. Also, patients can be enrolled if they have received prior antibacterial therapy that lacks in vitro activity against bacterial pathogens known to cause CABP.

Concomitant antibacterial therapy with an overlapping antimicrobial spectrum with the investigational drug should not be allowed during the trial. Patients who receive such therapy or require rescue antibacterial therapy might bias the trial and result in a false conclusion of noninferiority for any endpoint. For trials that use the endpoint of

improvement in clinical symptoms, patients who receive concomitant antibacterial therapy or rescue antibacterial therapy should be excluded from the evaluable population and considered failures in the intent-to-treat (ITT) and the microbiological intent-to-treat (micro-ITT) populations.

5. Efficacy Endpoints

Recommended efficacy endpoints to be considered for CABP trials are: a) an endpoint based on improvement in clinical symptoms; or b) an endpoint of all-cause mortality.

a. An endpoint based on improvement in clinical symptoms (e.g., chest pain, frequency or severity of cough, amount of productive sputum, difficulty breathing) at day 3 to 5 after randomization and initiation of trial drugs (enrollment)

- *Clinical success on improvement in symptoms:* Patients with improvement in at least 2 clinical symptoms of CABP compared to baseline (assessed as part of the inclusion criteria described in section III.B.3) and no worsening of other clinical symptoms and no new symptoms of CABP, at day 3 to 5 after enrollment (e.g., patients with improvement from moderate cough to mild cough and improvement from severe chest pain to moderate chest pain, while maintaining mild sputum production and mild shortness of breath that is not worsening)

- *Clinical failure on improvement in symptoms:* Patients who died or patients who do not meet the criteria for success at day 3 to 5 after enrollment (e.g., patients with improvement in only one clinical symptom and no improvement or worsening in other clinical symptoms)

A PRO instrument or DDT should be used to measure patient symptoms (e.g., chest pain, frequency or severity of cough, amount of productive sputum, difficulty breathing). Other symptoms may be included in the development of a PRO of DDT (chills/rigors/"feverishness", functional abilities such as eating or walking, or other clinical symptoms).

Because a PRO instrument or DDT has not been qualified by the FDA for this indication, exploratory testing of a well-developed PRO instrument or DDT in phase 2 or other clinical studies is encouraged and could lead into justifying its use to support primary endpoints in phase 3 trials. Development of the new instrument should begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocols. If the PRO or DDT has not yet been qualified as a primary endpoint, it may be appropriate to evaluate its use for assessment of secondary endpoints. Meanwhile, the endpoint of improvement in clinical symptoms as described above may be used as the interim primary efficacy endpoint while work to qualify a new PRO or DDT is ongoing.[5]

[5] For more information regarding the development of such outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and draft guidance for industry *Qualification of Drug Development Tools* (reference 13 on page 5). For an

b. An endpoint of all-cause mortality at 28-days after enrollment can be used as a primary efficacy endpoint in clinical trials of CABP

- *Clinical success.* Patients who are alive 28 days after enrollment.

- *Clinical failure.* Patients who have died within 28 days after enrollment.

c. Secondary endpoints in clinical trials of CABP

For clinical trials in which an interim endpoint of improvement in clinical symptoms is used, and a PRO or DDT has not been qualified for use, an essential secondary endpoint is the improvement or stabilization of clinical signs, as described below:

- *Clinical success on improvement/stabilization of signs:* improvement or stabilization of all vital signs and other objectively measured signs (e.g., oxygenation) that are sustained over the previous 24 hours at day 3 to 5 after enrollment, and no worsening in other clinical signs of CABP at baseline enrollment, and no new signs of CABP[6] (e.g., a patient with baseline RR of 24 per minute has decreased to 16 per minute; blood pressure remains stable at the patient's pre-illness blood pressure of 120/80 mmHg; heart rate with baseline of 120 per minute has decreased to 80 per minute; and baseline tympanic temperature of 38.9 degrees Celsius has decreased to 37.9 degrees Celsius; and at baseline required 4 liters of oxygen by nasal cannula to maintain normal arterial oxygenation and a day 3 to day 5 is maintaining normal arterial oxygenation by breathing room air).

- *Clinical failure on improvement/stabilization of signs.* Patients who died or patients who do not meet the criteria for clinical success at day 3 to 5 after enrollment (e.g.; patients with persistent body temperature elevations to greater than 38.0 degrees Celsius; patients with RR maintained at greater than 24 breaths per minute).

Even though the timing of a trial's primary efficacy endpoint may be at day 3 to day 5 after enrollment, it is essential to evaluate patients during the entire course of therapy and observation after completion of therapy to document as a secondary endpoint the proportion of patients who ultimately achieve clinical success after receiving the full course of the investigational drug. The assessment of continued clinical success or clinical failure should be assessed at a fixed time point that captures the end of treatment.

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interim efficacy endpoint based on improvement in symptoms, the description of how patients characterize their symptoms as "absent", "mild", "moderate", and "severe" should be included in the protocol.

[6] Improvement or stabilization of vital signs should be defined in the protocol. For example, see table 10 "Criteria for Clinical Stability" in: Mandell LA, Wunderink RG, Anzueto A, et. al., 2007. Infectious Disease Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis; 44: S27-72.

Another fixed time point that captures continued clinical success at 10 to 14 days following completion of treatment is recommended.

- *Clinical success:* Patients with resolution of clinical symptoms and resolution of clinical signs attributable to CABP at the end of treatment (and at 10 to 14 days following completion of treatment) and who did not receive other nonstudy antibacterial drugs for treatment of CABP.

- *Clinical failure:* Patients who have died or who have new or persistent clinical symptoms or clinical signs attributable to CABP at the end of treatment (and at 10-14 days following completion of treatment) including patients who received nonstudy antibacterial drugs for treatment of CABP.

The results of these secondary analyses (improvement or stabilization of clinical signs at day 3 to day 5, clinical success or clinical failure at end of treatment, and clinical success or clinical failure at 10-14 days following completion of treatment) should be compared to the results of the primary endpoint when the primary endpoint is improvement in clinical symptoms at day 3 to 5 after enrollment. While prespecified success or failure criteria are not required on the secondary endpoints, it is possible to identify in the statistical analysis plan the particular analyses when the trial is successful on its primary endpoint. Using sequential approaches or multiplicity corrections, statistically valid conclusions may be reached on secondary endpoints. Observations of imbalances between treatment groups on the secondary endpoints (improvement or stabilization of clinical signs at day 3 to day 5, clinical success or clinical failure at end of treatment, and clinical success or clinical failure at 10-14 days following completion of treatment) should be fully evaluated.

We recommend that all patients have a day 28 safety assessment for mortality (note that the day 28 assessment for mortality would be the primary outcome measure for a trial with 28-day all-cause mortality as the primary endpoint).

6. Clinical Trial Procedures and Timing of Assessments

a. Entry visit

At the entry visit, the following information should be captured and recorded on the case report form:

- History and physical examination

- Baseline symptoms

- Baseline vital signs including heart rate, respiratory rate, temperature, blood pressure

- Baseline signs including baseline oxygen saturation or partial pressure of oxygen on room air, if feasible

- Chest X ray

- Results of a clinical severity scoring system

- Microbiologic specimens: adequate sputum specimens as determined by Gram stain (see section III.B.3.a., Clinical, radiographic, and microbiologic criteria), sputum culture, blood cultures, other rapid diagnostic tests as appropriate

- Laboratory tests: hematology, chemistry, and others as appropriate

b. Daily visits after enrollment

Each patient should have on-therapy assessments of signs and symptoms. Because we recommend enrolling patients with a greater severity of pneumonia that most likely results in hospitalization (e.g., a PORT score of III or higher), daily study visits during hospitalization should be practicable and included in the protocol. The frequency of study visits after discharge from the hospital depends on whether a time-to-resolution secondary endpoint is assessed (i.e., daily assessments during the entire course of therapy for time-to-resolution analyses). Patients should be clinically evaluated by the investigator at a 48- to 72-hour visit to ensure that there is no clinical worsening at this time, in addition to the visit at day 3 to day 5 in trials where the improvement in clinical symptoms at this time point is the primary endpoint.

Assigning clinical failure and permitting use of rescue antibacterial drug therapy should be reserved for patients who are worsening or not improving on their assigned treatment arm; specific criteria to initiate rescue therapy in these patients should be included in the protocol. Appropriate specimens for microbiologic evaluation should be obtained in these patients before instituting the new antibacterial drug therapy. It is important that investigators distinguish between patients who are worsening or not improving (i.e., where antibacterial drug rescue therapy is appropriate) from patients who are slow to improve but may still remain on their original treatment assignment. In the case of clinical failure where patients are worsening or not improving, therapy should be changed to an appropriate alternative antibacterial drug rescue therapy for CABP, with other therapeutic modifications as necessary. Patients who receive rescue therapy should continue to have protocol-specified assessments identical to patients who continue to receive their originally assigned treatment but should be assigned as treatment failures on secondary endpoints at end of treatment and at 10-14 days following completion of treatment. Patients characterized as a failure on the symptom response endpoint at day 3 to day 5 yet are slow to improve and remain on their original treatment assignment for the remainder of the trial (e.g., did not meet criteria for administration of rescue antibacterial drug therapy) may be evaluated on the secondary endpoints at end of treatment and at 10-14 days following completion of treatment for continued clinical success or clinical failure.

c. Visit at end of treatment

Patients should be evaluated clinically at a prespecified time point that corresponds to the completion of antibacterial drug treatment to evaluate continued clinical success.

At this visit, the following information should be captured and recorded on the case report form:

- History and physical examination
- Symptoms including the documentation of resolution by the patient
- Vital signs including heart rate, respiratory rate, temperature, blood pressure
- Oxygen saturation or partial pressure of oxygen on room air (or baseline supplemental oxygen), if feasible
- Chest X ray
- Laboratory tests: hematology, chemistry, and others as appropriate

If the study drug needs to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol. Patients who were characterized as a success on a symptom improvement endpoint at day 3 to day 5 of therapy should remain characterized as a success at this early time point regardless of the outcome of subsequent assessments. Patients who subsequently fail to demonstrate continued clinical improvement or with progression of symptoms or worsening of clinical signs during the remainder of therapy should be considered failures on secondary efficacy endpoints at the end of treatment and alternative antibacterial drug rescue therapy should be provided. While such patients should not be re-characterized as failures at the early time point at day 3 to day 5 of therapy, the outcomes on the secondary endpoints at the end of treatment will be considered as an essential secondary endpoint assessment. Microbiologic specimens should be obtained at the timing of clinical failure: adequate sputum specimens as determined by Gram stain (see section III.B.3.a., Clinical, radiographic, and microbiologic criteria), sputum culture, blood cultures, or other rapid diagnostic tests as appropriate.

d. Visit at 10 to 14 days after completion of treatment

Patients should be followed for a period of time after completion of antibacterial drug treatment to assess for continued clinical success and capture mortality data (e.g., 28-day all-cause mortality). For clinical trials designed for the primary endpoint of 28-day all-cause mortality, this study visit should be at a fixed time point at 28 days following enrollment. Investigators should perform an assessment at this visit that includes a medical history, a

physical examination, appropriate laboratory evaluations, and identification of any new adverse events.

7. Statistical Considerations

The trial hypotheses and the analysis methods should be stated in the protocol and the statistical analysis plan. These should preferably be finalized before trial initiation. In certain circumstances, changes in the statistical analysis plan may be considered if the trial remains blinded to treatment assignments; however, documenting the maintenance of the blind can prove difficult. Any proposed changes should be discussed with us in advance of the change. The trials should be adequately powered to detect differences between treatment arms if differences exist. If sponsors choose to test multiple hypotheses, they should address issues related to the potential inflation of false positive results (overall type I error rate) because of multiple comparisons. These issues should be discussed with us during protocol development, and if any subsequent changes are considered they should be discussed with us before incorporation into the statistical analysis plan.[7]

a. Analysis populations

The following definitions apply to various analysis populations in CABP clinical trials:

- Safety population — All patients who received at least one dose of drug during the trial.

- ITT population — All patients who were randomized.

- Micro-ITT population (microbiological intent-to-treat population) — All randomized patients who have a baseline bacterial pathogen known to cause CABP against which the test drug has antibacterial activity. This includes bacterial pathogens identified in blood, appropriate sputum specimen, or other nonculture methods of detection of bacterial pathogens (e.g., urinary antigen test). Patients should not be excluded from this population based upon events that occur postrandomization (e.g., noncompliance or loss to follow-up).

- Clinically evaluable or per-protocol populations — Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.

- Microbiologically evaluable populations — Patients who meet the definition for the micro-ITT population and who follow important components of the trial as specified in the protocol.

[7] See ICH E9 and ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

For noninferiority trials using an endpoint of all-cause mortality or an endpoint of improvement in patient symptoms at day 3 to day 5, we recommend an approach where there are co-primary analyses; an analysis of each of the 2 trials using an ITT population and an analysis of the pooled micro-ITT populations (see main background document and below section c. Sample size considerations). Trials should be enriched for patients with bacterial disease, for example, by enrolling patients with a greater severity of disease. Hence, the ITT analyses are informative. To provide an analysis of only those patients with documented bacterial infections, an analysis of the pooled micro-ITT populations from the 2 trials should be performed. In addition, consistency of results should be evaluated in the clinically evaluable populations and the microbiologically evaluable populations. For superiority trials, the ITT population may be considered the primary analysis population; a bacterial pathogen should be documented in at least 25% of the patients in the trial.

b. Noninferiority margins

Based on a review of the historical data, we believe that noninferiority trials are appropriate for the CABP indication. This issue was discussed at the Anti-Infective Drugs Advisory Committee meetings in April 2008 and December 2009. The noninferiority margins can be justified based on historical evidence of the treatment effect of antibacterial therapy on an all-cause mortality endpoint. In addition, an endpoint based on improvement in clinical symptoms at day 3 to 5 may have noninferiority justification based on the large treatment effect in patients with lobar or pneumococcal pneumonia (see section 8, Noninferiority Margin Justification for a Symptom Response Endpoint). Sponsors should justify the noninferiority margin for their proposed trial design and population enrolled. In the final trial report, sponsors should address issues relating to the noninferiority margin as it applies to their trial populations.

c. Sample size considerations

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate, the noninferiority margin (for a noninferiority trial), or the amount by which the study drug is expected to be superior (for a superiority trial). The appropriate sample size should be estimated using a two-sided Type I error (α) of 0.05 (α=0.05).

One approach to improve practicability of sample sizes in clinical trials of CABP is to greatly enhance the proportion of patients with microbiological diagnosis for a bacterial etiology of CABP. For example, this proportion could be increased by including patients who have evidence of CABP based on nonculture methods (e.g., a positive result on a *S. pneumoniae* urinary antigen test). In addition, the potential for a numerically higher treatment effect of the investigational drug over the active-control drug (e.g., a point estimate difference in treatment effect of 5 percent or higher, if achievable) would significantly reduce the estimates for sample sizes.

Using an interim endpoint of improvement in symptoms at day 3 to day 5, we assumed the rate of success is 80 percent. We also assumed a 2-sided type 1 error (α) of 0.05 and type 2 error (β) of 0.10 (power 0.90) for each of the ITT analyses and overall the type 2 error (β) of 0.20 (power 0.80)[8], and a noninferiority margin of 10 percent for the ITT analyses and a noninferiority margin of 15 percent for the micro-ITT analysis. It may be reasonable to expect that 27% of patients will have microbiological diagnosis of a bacterial etiology for CABP. In this case, a total of approximately 344 patients per arm should be enrolled in each trial using a 1:1 randomization to investigational drug or active-control drug. The total number of patients for both trials would be approximately 1376 patients (344 patients per arm in each of two trials). Appendix 3 contains several tables of sample size estimates based on different assumptions regarding overall power and noninferiority margins.

In summary, noninferiority would be demonstrated based on a co-primary hypothesis (H1 and H2):

> H1: demonstration of noninferiority (using 10% margin) independently for both trials in the ITT populations
>
> H2: demonstration of noninferiority (using 15% margin) for the weighted pooling of the micro-ITT population as a single analysis.

d. Secondary endpoints and other analyses of interest

Essential secondary endpoints include the evaluation of improvement or stabilization of clinical signs at day 3 to day 5 and the evaluation of sustained clinical responses at the end of therapy and at 10 to 14 days after completion of therapy. Observed differences between the results of the secondary endpoints and the primary endpoint should be fully explored.

Sponsors can present other secondary analyses on other endpoints of interest such as:

- Mortality and clinical responses in bacteremic versus nonbacteremic patients
- Responses based on patient demographics such as age, geographic region, underlying renal impairment, and microbiologic etiology
- Time-to-resolution of clinical signs and symptoms

8. Noninferiority Margin Justification for a Symptom Response Endpoint

There are data to support a noninferiority trial design using an all-cause mortality endpoint, as described in the appendix of the currently available draft guidance on CABP. The following provides a noninferiority justification for a symptom response endpoint.

[8] In the sample size calculation the power is estimated at 0.904 for each of the two ITT analyses and 0.951 for the pooled micro-ITT analysis; for all analyses the power is estimated to be 0.80.

Direct extrapolation of treatment effect from historical studies to present-day CABP clinical trials is difficult. The historical studies lacked blinding and randomization as currently defined. There is also considerable uncertainty regarding the similarity of patient populations from historical studies to populations in current clinical trials. For example, patients today may have different comorbidities and risk factors for pneumonia, or may have received pneumococcal vaccine. Additionally, improved standards of medical care today result in improved outcomes and lower mortality rates (e.g., care in an intensive care unit, mechanical ventilation, hemodynamic support). Finally, the modern conceptual framework of a clinical endpoint on how a patient feels or functions were not fully reflected in historical studies evaluating clinical responses. Historical papers did not evaluate improvement in clinical symptoms separately, but improvement in both signs and symptoms was included in the overall clinical responses. This underscores the importance of doing developmental work on endpoint assessments for a symptom-based endpoint prior to phase 3 trials.

Another area of uncertainty is the spectrum of bacterial pathogens that cause CABP today in comparison to the early mid-twentieth century. In most of the historical studies and historical-controlled clinical trials, CAP was considered synonymous with pneumococcal pneumonia because *S. pneumoniae* was identified, whereas in recent CAP clinical trials, less than 20 percent of the total patient populations had documented *S. pneumoniae*.[9] CAP is also caused by other pathogens such as *H. influenzae*, *S. aureus*, and *M. catarrhalis*; atypical bacteria such as *M. pneumoniae* and *C. pneumoniae*; and *Legionella* species, as well as respiratory viruses. Limited information is available on antibacterial treatment effect in CAP caused by *M. pneumoniae*, whereas for pathogens such as *C. pneumoniae*, the size of the treatment effect remains unknown.

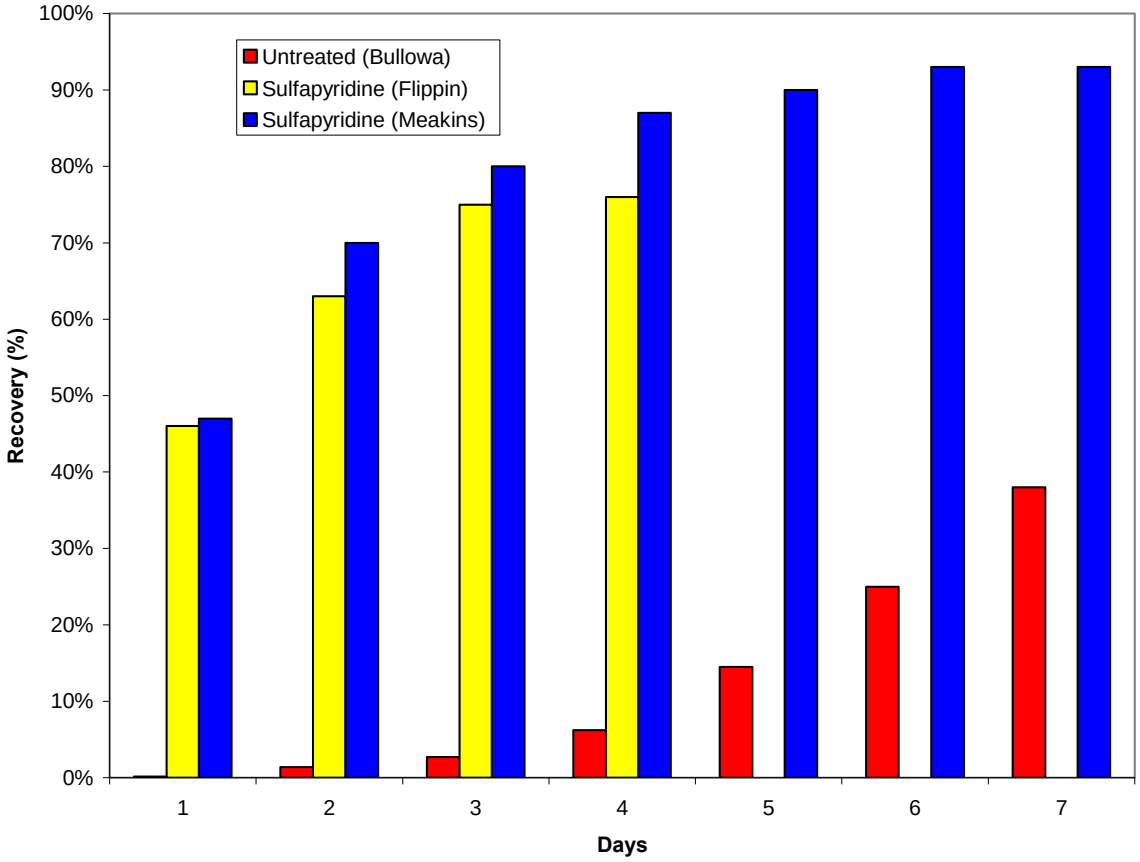
Studies conducted at the time of the introduction of antibacterial drug therapy described clinical responses among untreated patients and patients treated with antibacterial drugs. These observational studies provide an estimate of the effect of antibacterial drugs on clinical response endpoints other than mortality.

Several papers described the clinical course of patients with pneumococcal pneumonia in a similar way; patients were recorded as having a successful clinical outcome by the demonstration of fever resolution and accompanying improvement and resolution of other signs and symptoms of pneumonia. For example, a description in one of the papers stated, "This fall in temperature was in all cases accompanied by a conspicuous reduction in the pulse and respiratory rates, and the patients were improved subjectively".[10] One study described the clinical course of patients that did not receive antibacterial drug therapy, while two other studies included patients that received antibacterial drug therapy. Figure 1

[9] Higgins, K, M Singer, T Valappil, S Nambiar, D Lin, and E Cox, 2008, Overview of Recent Studies of Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3) S150-S156.
[10] Meakins JC, Hanson FR. 1939. The treatment of pneumoccic pneumonia with sulfapyridine. The Canadian Medical Association Journal; April: 333-336.

compares the 3 studies in the rates of clinical recovery, defined generally as the improvement in both clinical signs and symptoms.[11,12]

Figure 1: Rates of clinical recovery recorded at each day



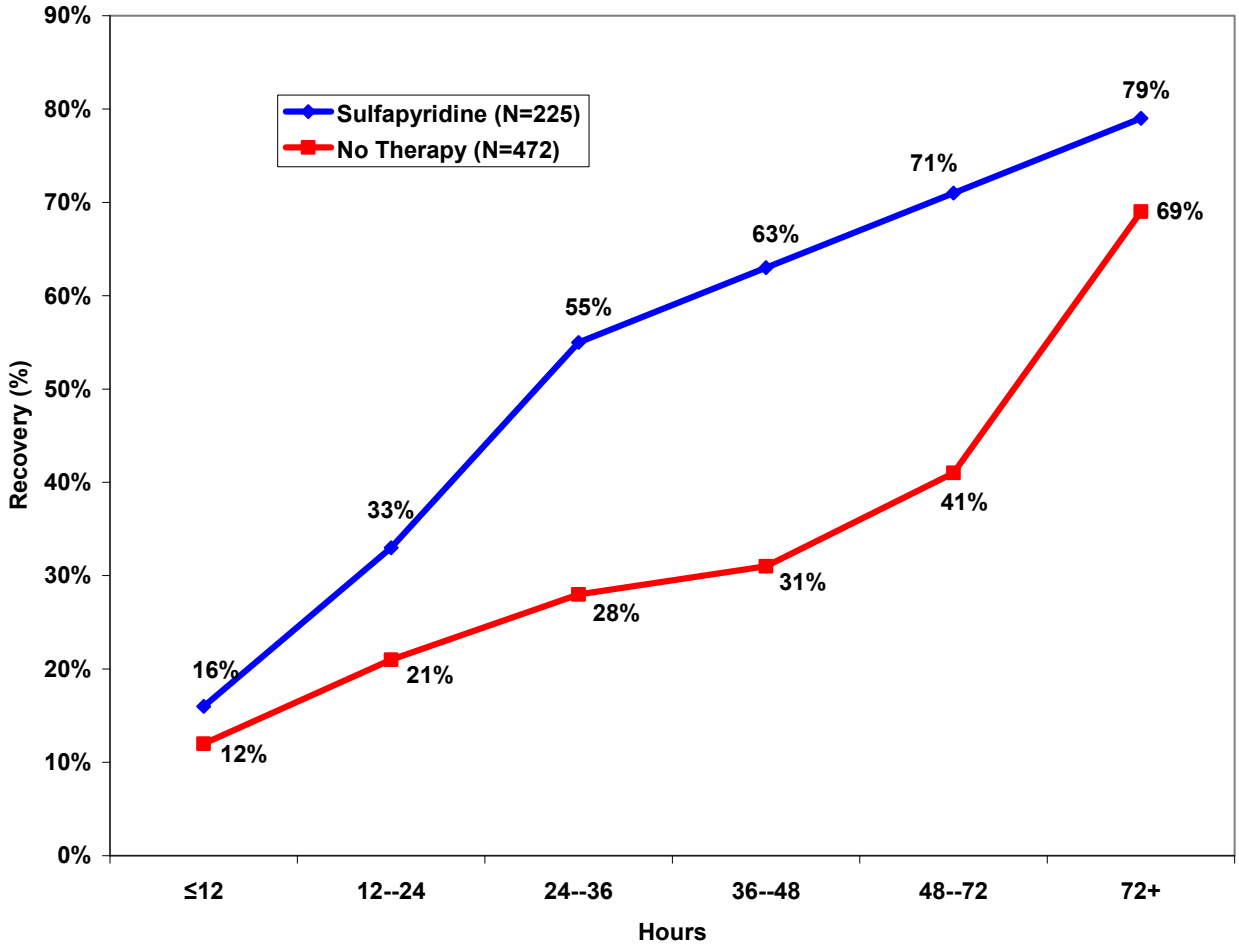
In this example of the 3 studies, the point estimate for treatment differences on clinical recovery at day 3, comparing the two treatment studies with the study of untreated patients, were 72% and 77%, respectively.

Figure 2 below shows the rates of clinical recovery in an observational study of patients with pneumococcal pneumonia that received antibacterial drug therapy (sulfapyridine) and a group of patients that received no specific therapy. Clinical recovery was defined as "permanent drop in oral temperature below 100°F, with subsidence of other symptoms of

[11] Bullowa JGW 1937. The course, symptoms and physical findings. In: Bullowa JGW, editor. The management of pneumonias. Oxford University Press; New York.
[12] Flippin HF, Lockwood JS, Pepper DS, Schwartz L. 1939. The treatment of pneumococcic pneumonia with sulfapyridine. JAMA;112:529-534.

acute infection." [13] Time points at 36 to 48 hours and 48 to 72 hours after initiation of therapy demonstrate the greatest treatment effect of clinical recovery. The treatment difference is 29% (95% confidence interval 22%, 37%) at the 48 to 72 hour time point. Clinical observations that were reported at *any* time after the 48-72 hour assessment are displayed as "72+" in Figure 2.

Figure 2: Rates of clinical recovery of acute bacterial pneumonia (Finland 1940)



A study in pediatric patients with bacterial pneumonia presented data from two treatment groups, one with antibacterial drug treatment and the other without antibacterial drug treatment. The time to observed clinical improvement, time to temperature resolution, and time to full clinical recovery was assessed by the clinician. For each of these evaluations of clinical responses, there were clear differences observed between the treatment groups that favored the antibacterial drug therapy.[14]

[13] Finland M, Spring WC, Lowell FC. 1940. Specific treatment of the pneumococcic pneumonias; an analysis of the results of serum therapy and chemotherapy at the Boston City Hospital from July 1938 through June 1939. Annals of Internal Medicine;13:1567-1593.

[14] Wilson AT, Spreen AH, Cooper ML, et al. 1939. Sulfapyridine in the treatment of pneumonia in infancy and childhood. JAMA; 112: 1435-1439.

The clinical response endpoints that were evaluated in each of these studies were not well-defined. The studies evaluated both clinical signs and symptoms together. A large treatment effect was observed at the early time point in the course of therapy, i.e. days 3 to 5 after initiation of therapy, for an endpoint that included improvement in both clinical signs and symptoms. The studies show that the treatment differences become smaller at time points beyond days 3 to 5 of therapy. The strengths of these studies for use as an estimate of M1 include the following:

- The studies documented bacterial pneumonia, all as *S. pneumoniae*
- Except for the observations from the Finland study, with antibacterial drug treatment the mortality rates in the studies were generally low (between 3 percent and 7 percent); low mortality rates have been observed in more recently conducted clinical trials of CAP and this supports the constancy assumption for clinical response endpoints
- The studies were conducted at the first introduction of antibacterial drugs for treatment of bacterial pneumonia when the treatment effect on reduction in mortality was observed
- The estimate of the treatment difference appears to be substantially large
- The clinical response endpoint of symptom improvement reflects a present-day conceptual framework for a clinical endpoint on how a patient feels, functions, or survives

The limitations of these studies include the following:

- The studies were observational and included a relatively small number of patients
- Cross-study comparisons create a greater level of uncertainty in the estimate of a treatment differences
- The clinical response evaluations were not clearly defined and the time point for assessment of the greatest difference in clinical response varied between day 3 to day 5
- The clinical response evaluations included improvement in both clinical signs and symptoms together and did not evaluate improvement in clinical symptoms separately

Noninferiority margin for the endpoint of improvement in clinical symptoms

The treatment difference appears to be large for an endpoint based on improvement in clinical symptoms earlier in the course of therapy for CABP. However, given the variability in the treatment differences (from a point estimate of 30% treatment difference at a 48 to 72 hour time point noted on figure 2, to a point estimate of 77% treatment difference at day 3 noted on figure 1), the determination of M1 as a precise numerical value is difficult to determine. Yet an M1 of at least 20% appears to be an appropriate estimate, accounting for the uncertainties with the historical data and allowing for discounting of the treatment difference. The selection of a noninferiority margin (M2) of 10% might be appropriate for the endpoint of improvement in clinical symptoms at day 3 to 5 following enrollment in the ITT population, and as noted in a pooled micro-ITT

population a noninferiority margin of 10%, 12.5%, or 15% may be considered for this analysis.

9. Clinical Responder Endpoint at a Test of Cure Time Point

We examined the information from two active-controlled trials of daptomycin in patients with CAP.[15] The primary endpoint was an assessment of clinical cure at a "test-of-cure" (TOC) study visit 7-14 days after completing treatment, with cure defined as the absence of clinically significant symptoms or improvement in symptoms such that no additional therapy was required.

Using this endpoint at a TOC study visit, daptomycin was not shown to be effective for the treatment of CAP, with ceftriaxone as the active-control drug in two trials (the first trial completed enrollment while the second trial stopped enrollment before completion because the first trial did not meet predetermined criteria for noninferiority). Additional nonclinical studies were conducted and found that daptomycin's antibacterial effect is diminished in the presence of pulmonary surfactant.[16] Thus, there was a biologically plausible reason for the difference in the efficacy response rate between the treatment groups in these two trials. This raised the possibility of considering these trials to be used as a measure of the effect of an active-control treatment over an inferior treatment for CABP for an estimate of M1 using a TOC time point.

The ITT Population was defined as all subjects who received any study drug. In addition, PORT Risk Class I and II subjects were enrolled in the daptomycin trials and comprised approximately 40 percent of ITT patient population. The following tables 1 and 2 show the results of the two daptomycin trials, by PORT Risk Class and by prior antibiotic use. Antibacterial drugs considered long-acting included azithromycin, levofloxacin, ceftriaxone, and lincomycin. Antibacterial drugs considered short-acting included penicillins, tetracyclines, and trimethoprim-sulfamethoxazole. An important patient population included the subgroup of patients that were more seriously ill (PORT III or IV) and did not receive prior long-acting antibacterial drugs. Table 3 shows estimated treatment effects and confidence intervals, including the subgroup of patients more severely ill that did not receive prior long-acting antibacterial drugs, when using the DerSimonian and Laird random effects model.[17]

[15] Pertel PE, Bernardo P, Fogarty C, et al. 2008. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis; 46(8):1152-1156.
[16] Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. 2005. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. J Infect Dis;191(12):2149-2152.
[17] DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Controlled Clinical Trials 7:177-188.

Table 1: Clinical Cure Rates in DAP-00-05, ITT Population

	Daptomycin	Ceftriaxone	Diff	95% CI
All Risk Classes				
All subjects	231/326 (70.9%)	258/335 (77.0%)	-6.2%	(-12.8%, 0.5%)
No long-acting prior therapy	179/248 (72.2%)	212/261 (81.2%)	-9.0%	(-16.4%, -1.7%)
No prior therapy	111/155 (71.6%)	142/173 (82.1%)	-10.5%	(-19.6%, -1.4%)
Risk Class III-IV				
All subjects	131/192 (68.2%)	128/175 (73.1%)	-4.9%	(-14.1%, 4.4%)
No long-acting prior therapy	**101/145 (69.7%)**	**103/130 (79.2%)**	**-9.6%**	**(-19.7%, 0.8%)**
No prior therapy	67/95 (70.5%)	68/84 (81.0%)	-10.4%	(-22.7%, 2.3%)

Table 2: Clinical Cure Rates in DAP-00-08, ITT Population

	Daptomycin	Ceftriaxone	Diff	95% CI
All Risk Classes				
All subjects	62/87 (71.3%)	68/86 (79.1%)	-7.8%	(-20.6%, 5.1%)
No long-acting prior therapy	57/80 (71.2%)	58/76 (76.3%)	-5.1%	(-18.7%, 8.8%)
No prior therapy	43/66 (65.2%)	48/61 (78.7%)	-13.5%	(-28.6%, 2.2%)
Risk Class III-IV				
All subjects	33/55 (60.0%)	50/61 (82.0%)	-22.0%	(-37.7%, -5.6%)
No long-acting prior therapy	**30/50 (60.0%)**	**42/53 (79.2%)**	**-19.2%**	**(-36.1%, -1.5%)**
No prior therapy	21/41 (51.2%)	33/40 (82.5%)	-31.3%	(-49.3%, -11.1%)

Table 3: Meta-Analysis of Clinical Cure Rates in DAP-00-05 and DAP-00-08

Daptomycin - Ceftriaxone		95% CI
All subjects	-6.5%	(-12.4%, -0.6%)
No long-acting prior therapy	-8.1%	(-14.6%, -1.7%)
No prior therapy	-11.3%	(-19.1%, -3.4%)
Risk Class III-IV		
All subjects	-12.1%	(-28.6%, 4.4%)
No long-acting prior therapy	**-12.1%**	**(-20.1%, -3.2%)**
No prior therapy	-19.5%	(-39.8%, 0.8%)

For patients in PORT Risk Class III-IV, note that the largest point estimate treatment difference was observed in the smaller subgroup that did not receive any prior antibacterial drug therapy but wide 2-sided 95% confidence intervals that move across zero prevent a conservative estimate of a treatment difference. Larger sizes of the subgroup that included short-acting antibacterial drug therapy (no long-acting prior therapy) result in narrower estimates of the 2-sided 95% confidence interval. In this subgroup, the estimated difference in clinical cure rates between daptomycin and ceftriaxone was 12.1%, with a 95% confidence interval of (-20.1%, -3.2 %). Based on the upper limit of this confidence interval, the daptomycin trials may provide an estimate of a treatment difference at approximately 3% for the clinical response endpoint at TOC.

These analyses are based on post-hoc subgroup analyses and are at best considered exploratory. Even the selection of M1 and M2 at 3% without discounting and without preserving any portion of the treatment effect (because daptomycin may have some level of activity) would not result in a trial size of practicable proportions. Therefore, we do not recommend the use of the daptomycin trials for the purpose of defining M1 and selecting a noninferiority margin for a TOC clinical response endpoint. Another important finding from those studies was the influence of prior effective antibacterial drug therapy on a successful outcome, as discussed in the main background document.

APPENDIX 3: Tables of Sample Sizes for CABP Clinical Development Programs

Using a primary endpoint of improvement in clinical symptoms at day 3 to day 5, we assumed the rate of success in the control group is 80 percent. We also assumed a rate of microbiological confirmation (micro-ITT population) to be 27%. The following table shows the power at different sample sizes for a clinical development program of 2 noninferiority trials, where a noninferiority margin of 10% is used for the ITT analysis population and a noninferiority margin of 15% is used for the pooled micro-ITT population.

Table 1: Sample sizes for 15% noninferiority in the pooled micro-ITT analysis and 10% noninferiority in each of the ITT analysis of the two trials

Sample Size			Power to meet non-inferiority requirements for:			
Per Arm	Per Trial	Per Program	ITT analysis in a single trial	ITT analysis in both trials	MITT analysis in pooled trials	All requirements: ITT analysis in both trials and MITT analysis in pooled trials
330	660	1320	89.7	80.4	94.5	77.7
340	680	1360	90.4	81.7	95.1	79.3
350	700	1400	91.2	83.2	95.5	80.8
360	720	1440	92.0	84.6	96.0	82.5
370	740	1480	92.6	85.7	96.5	83.8
380	760	1520	93.2	86.8	96.9	85.1
390	780	1560	93.8	88.0	97.2	86.3
400	800	1600	94.3	89.0	97.5	87.5
410	820	1640	94.8	89.9	97.7	88.5
420	840	1680	95.3	90.8	98.0	89.5
430	860	1720	95.7	91.5	98.2	90.4

For a program where 80% power is selected to meet all requirements (ITT analysis populations for each trial and pooled micro-ITT population and a noninferiority margin of 15% for the micro-ITT population), the sample size is approximately 344 subjects per arm in each trial (a total of 688 subjects per trial and 1376 subjects for the CABP development program). When a power of 90% is selected to meet all requirements, the sample size is approximately 430 subject per arm or approximately 1720 subjects per development program.

Using the same assumptions of 80% success rate and 27% microbiological confirmation, except that the noninferiority margin is 12.5% for the micro-ITT analysis instead of 15%, the following table shows the power at different sample sizes:

Table 2: Sample sizes for 12.5% noninferiority in the pooled micro-ITT analysis and 10% noninferiority in each of the ITT analysis of the two trials

Sample Size			Power to meet non-inferiority requirements for:			
Per Arm	Per Trial	Per Program	ITT analysis in a single trial	ITT analysis in both trials	MITT analysis in pooled trials	All requirements: ITT analysis in both trials and MITT analysis in pooled trials
380	760	1520	93.2	86.9	88.9	79.5
390	780	1560	93.8	88.0	89.6	80.9
400	800	1600	94.4	89.0	90.4	82.3
410	820	1640	94.8	89.9	91.0	83.5
420	840	1680	95.3	90.8	91.6	84.7
430	860	1720	95.7	91.5	92.2	85.8
440	880	1760	96.0	92.2	92.8	86.8
450	900	1800	96.4	93.0	93.3	87.9
460	920	1840	96.7	93.5	93.7	88.7
470	940	1880	97.0	94.1	94.2	89.5
480	960	1920	97.2	94.6	94.7	90.3

For a program where 80% power is selected to meet all requirements (ITT analysis populations for each trial and pooled micro-ITT population and a noninferiority margin of 12.5% for the micro-ITT analysis), the sample size is approximately 384 subjects per arm in each trial (a total of 768 subjects per trial and 1536 subjects for the CABP development program). When 90% power is selected to meet all requirements, the sample size is enhanced to approximately 475 patients per arm for each trial, or approximately 1900 subjects for the CABP development program.

Using the same assumptions of 80% success rate and 27% microbiological confirmation, except that the noninferiority margin is 10% for the micro-ITT analysis, the following table shows the power at different sample sizes:

Table 3: Sample sizes for 10% noninferiority in the pooled micro-ITT analysis and 10% noninferiority in each of the ITT analysis of the two trials

Sample Size			Power to meet non-inferiority requirements for:			
Per Arm	Per Trial	Per Program	ITT analysis in a single trial	ITT analysis in both trials	MITT analysis in pooled trials	All requirements: ITT analysis in both trials and MITT analysis in pooled trials
480	960	1920	97.2	94.5	81.2	78.4
496	992	1984	97.6	95.3	82.5	80.0
512	1024	2048	97.9	95.9	83.6	81.4
528	1056	2112	98.2	96.5	84.7	82.8
544	1088	2176	98.5	97.0	85.8	84.1
560	1120	2240	98.7	97.4	86.7	85.2
576	1152	2304	98.9	97.8	87.7	86.4
592	1184	2368	99.0	98.1	88.5	87.4
608	1216	2432	99.2	98.4	89.3	88.4
624	1248	2496	99.3	98.6	90.1	89.2
640	1280	2560	99.4	98.8	90.8	90.0

For a program where 80% power is selected to meet all requirements (ITT analysis populations for each trial and pooled micro-ITT population and a noninferiority margin of 10% for the micro-ITT analysis), the sample size is approximately 496 subjects per arm in each trial (a total of 992 subjects per trial and 1984 subjects for the CABP development program). When 90% power is selected to meet all requirements, the sample size is enhanced to approximately 640 patients per arm for each trial, or approximately 2560 subjects for the CABP development program.

In summary, noninferiority would be demonstrated based on a co-primary hypothesis (H1 and H2):

H1: demonstration of noninferiority independently for both trials in the ITT populations

H2: demonstration of noninferiority for the weighted pooling of the micro-ITT population as a single analysis.

APPENDIX 4

Guidance for Industry

Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sumathi Nambiar, MD, MPH, at 301-796-1400.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2009
Clinical Antimicrobial
Revision 1

Guidance for Industry

Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Guidance for Industry[1]
Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of community-acquired bacterial pneumonia (CABP). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of CABP.[2] This guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products and pharmaceutical sponsors, the academic community, and the public.[3]

This guidance revises the draft guidance for industry *Community-Acquired Pneumonia — Developing Antimicrobial Drugs for Treatment* published in 1998. Once final, this guidance will be considered the FDA's current thinking regarding the development of drugs for the treatment of CABP. It also supersedes, with regard to the development of drugs to treat CABP, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective Drugs (Systemic)* and *Clinical Development and Labeling of Anti-Infective Drug Products*,[4] as well as

[1] This guidance has been prepared by the Office of Antimicrobial Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purpose of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated by CDER unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the divisions to discuss specific issues that arise during the development of antimicrobial drug products.

[4] See http://www.fda.gov/cder/guidance/old047fn.pdf and http://www.fda.gov/cder/guidance/old043fn.pdf, respectively.

the joint FDA/Infectious Disease Society of America's (IDSA's) *General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products*.[5])

For the purpose of this guidance, we assume that the majority of hospitalized patients will be initially treated with intravenous (IV) antibacterials and ambulatory patients will be treated with oral antibacterial drugs. However, this does not preclude the enrollment of hospitalized patients in oral drug trials. Additionally, patients in IV antibacterial trials may need to be enrolled in an emergency room setting to preclude use of prior antibacterial therapies.

This guidance does not address the development of drugs for other purposes or populations, such as treatment of patients with viral infections or atypical bacterial pathogens (e.g., *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*), hospital-acquired pneumonia, or ventilator-associated pneumonia. If sponsors wish to develop drugs with activity against these pathogens, they should discuss the trial designs with the FDA. As the science of this indication evolves and new information accumulates, this guidance may be revised.

This guidance does not contain discussion of the general issues of clinical trial designs or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[6] This guidance focuses on specific drug development and trial design issues that are unique to the study of CABP.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality. It is estimated that approximately one million episodes of CAP occur annually in adults 65 years of age and older in the United States. Overall mortality remains relatively high, ranging from 5.1 percent for patients hospitalized or treated in an ambulatory setting to 36.5 percent for patients treated in an intensive care unit.[7] Common etiologic agents of CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *M. pneumoniae*. Certain

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clin Infect Dis, Nov 15 (Suppl 1): S5-S32.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[7] Fine, MJ, MA Smith, CA Carson, SS Mutha, SS Sankey, LA Weissfeld, and W Kapoor, 1996, Prognosis and Outcomes of Patients with Community-Acquired Pneumonia: A Meta-Analysis, JAMA, 275:134-141.

respiratory viruses, and atypical bacterial pathogens such as *C. pneumoniae* and *L. pneumophila*, also cause CAP.

Since the FDA published draft guidance on the development of antimicrobial drugs for the treatment of CAP in 1998, there have been public discussions regarding clinical trial designs to study CAP, including an FDA-IDSA workshop and a meeting of the Anti-Infective Drugs Advisory Committee.[8] These discussions have focused on clinical trial designs for CAP and other important issues such as the following:

- Noninferiority versus superiority design
- Justification of an appropriate noninferiority margin
- Classification of severity of illness
- Classification of CAP based on hospitalization (inpatient versus outpatient)
- Enrollment criteria
- Application of appropriate diagnostic criteria, including microbiologic diagnosis
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of prior antibacterial drugs

Important changes from the 1998 draft guidance that are based on these discussions have been incorporated into the appropriate sections below.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Definition of CABP

The FDA's previous clinical definition of CAP in an immunocompetent adult patient was an acute infection of the pulmonary parenchyma associated with at least some symptoms of acute infection and accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales). The patient should not have been hospitalized or resided in a long-term care facility for 14 or more days before the onset of symptoms.

To better identify individuals most likely to have bacterial pneumonia and hence benefit from antimicrobial therapy, this guidance defines CABP in an adult patient as an acute infection of the pulmonary parenchyma associated with symptoms such as fever or hypothermia, chills, rigors, cough, chest pain, or dyspnea, accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph.

[8] See http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective.

2. Drug Development Population

The intended trial population should be patients 18 years of age and older with CABP. In addition to the clinical syndrome of bacterial pneumonia previously described, bacteriological confirmation of the etiologic agent (discussed later in this guidance) should be provided in at least 30 to 40 percent of enrolled patients.

3. Pharmacokinetic and Pharmacodynamic Considerations

New antibacterial drugs being studied for CABP should have nonclinical data documenting activity against the most commonly implicated pathogens for CABP (i.e., *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *Moraxella catarrhalis*).

Evaluation of the pharmacokinetic and pharmacodynamic characteristics of an antibacterial drug being developed for CABP can provide useful data to inform dose selection and dosing regimens that should be evaluated in subsequent clinical trials.

Investigation of the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of an antibacterial drug can begin in nonclinical studies. Dose fractionation studies, often conducted in a thigh infection model, can be useful in determining the PK/PD index best associated with activity for a new antibacterial drug. There are also other models such as in vitro hollow-fiber models and in vivo animal infection models (other than the thigh infection model) that can be used to identify or explore the PK/PD index best associated with antibacterial effect as well as the magnitude of the PK/PD index necessary to achieve the desired endpoint. Ideally, animal models of infection exploring antibacterial drug activity should be conducted in neutropenic and immunocompetent mice to evaluate antibacterial drug effect in the setting of either a compromised or intact immune system. Information regarding the pharmacokinetics and lung distribution of the test drug in the species being studied is important in interpreting pharmacodynamic data derived from the animal model.

In addition to thigh infection models, animal models of acute pneumonia have been developed in both mice and rats, particularly for *S. pneumoniae* infection for evaluation of antibacterial therapy.[9,10] The majority of pneumonia models initiate infection by direct instillation into nares and/or trachea, but lung infection also has been initiated using an aerosolization procedure.[11] Reproducible invasive lung infections are more difficult to induce with organisms such as *H. influenzae*.[12] Differences in the effect of animal lung secretions versus human lung secretions on

[9] Tessier, PR et al., 2002, Pharmacodynamic Assessment of Clarithromycin in a Murine Model of Pneumococcal Pneumonia, Antimicrob Agents Chemother, 46:1425-1434.

[10] Gavalda, J et al., 1997, Treatment of Experimental Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae* in Immunocompetent Rats, Antimicrob Agents Chemother, 41:795-801.

[11] Legget, J, 1999, Murine Models of Pneumonia Using Aerosol Infection, In: Zak O, Sande MA, eds., Handbook of Animal Infections: San Diego, Academic Press, 533-538.

[12] Miyazaki, S et al., 1997, New Murine Model of Bronchopneumonia due to Cell-Bound *Haemophilus influenzae*, J Infect Dis, 175:205-209.

149 the activity of the antibacterial should be evaluated.[13] Although animal models may contribute
150 to providing early proof of concept in the treatment of CABP (or for comparing in vivo activity
151 of different antimicrobials), the results should be carefully interpreted when used to help design
152 subsequent human trials. Animal models also can be used to explore antimicrobial activity
153 against resistant bacteria or specific bacterial serotypes that occur less commonly in clinical
154 trials.[14] Animal studies cannot, however, substitute for the clinical trials in patients with CABP
155 that must be conducted to evaluate drug safety and efficacy because clinical studies can be
156 conducted in patients with CABP.[15]
157
158 The results of PK/PD assessments in animals should be integrated with the findings from phase 1
159 pharmacokinetic studies to help identify the appropriate dosing regimens for evaluation in phase
160 2 and phase 3 clinical trials. A dose-response trial design should be considered as it allows
161 weighing the benefits and risks of various doses and can ensure that excessive doses (beyond
162 those that add to efficacy) are not used, offering some protection against unexpected and
163 unrecognized dose-related toxicity.[16]
164
165 Consideration should be given to obtaining blood samples from all patients in phase 2 and phase
166 3 clinical trials (*sparse sampling*) to allow for the estimation of drug exposure in each patient. A
167 retrospective exposure-response analysis based on the population pharmacokinetic model should
168 be performed to assess the relationship between exposure and observed clinical and
169 microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse
170 events also should be explored to identify potential risks with different dosing regimens (if
171 applicable) and specific patient populations.
172
173 *4. Dose Selection*
174
175 To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate
176 the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics,
177 safety and tolerability information from phase 1 clinical trials, and safety and efficacy
178 information from phase 2 dose-ranging clinical trials. Studies assessing drug penetration at the
179 site of action (e.g., epithelial lining fluid) may be helpful in defining doses that achieve
180 concentrations sufficient to exert an antibacterial effect. In addition, the pharmacokinetics of the
181 drug in specific populations (e.g., geriatric patients, patients with renal or hepatic impairment)
182 should be evaluated before initiation of phase 3 trials to determine whether dose adjustments are
183 necessary. This evaluation may prevent the exclusion of such patients from phase 3 clinical
184 trials.

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[13] Silverman, JA, LI Mortin, AD Vanpraagh, T Li, and J Alder, 2005, Inhibition of Daptomycin By Pulmonary Surfactant: In Vitro Modeling and Clinical Impact, J Infect Dis, 191:2149-2152.

[14] Bender, JM, K Ampofo, K Korgenski et al., 2008, Pneumococcal Necrotizing Pneumonia in Utah: Does Serotype Matter?, Clin Infect Dis, 46:1346-1352.

[15] 21 CFR 314.600 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.600)

[16] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* (http://www.fda.gov/cder/guidance/index.htm).

5. Efficacy Considerations

Either noninferiority or superiority trial designs can be used for this indication, but we do not believe that placebo-controlled trials can be ethically conducted for this indication, because placebo-treated patients would be exposed to serious risks.[17] The goal of CABP clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of CABP caused by bacterial pathogens such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, or *M. catarrhalis*. If sponsors wish to include additional organisms in clinical trials for this indication, they should provide data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in CABP. Patients with risk factors for infection with drug-resistant organisms such as methicillin-resistant *S. aureus* can be enrolled if the spectrum of activity of both the investigational drug and comparator includes the specific organism.

The number of clinical trials needed to support a CABP indication depends on the overall development plan for the drug under consideration. If the development plan for the drug has CABP as the sole indication, then it would be expected that two adequate and well-controlled trials would support effectiveness. If a drug is being developed for other respiratory infections, sponsors should discuss with the FDA whether other trials might lend support to a CABP indication. A trial in which most patients have documented bacterial pathogens (e.g., *S. pneumoniae*, *H. influenzae*, *S. aureus*, or *M. catarrhalis*) generally will provide the strongest evidence of efficacy. Although a documented bacterial etiology is important for all trial designs, it is particularly critical for noninferiority trials, because the noninferiority margin is based on the evidence from patients with microbiologically documented infections, primarily *S. pneumoniae*. Microbiological confirmation also permits analysis of treatment response by individual pathogen.

For drugs that have only an IV formulation available, we recommend that sponsors conduct trials with the IV formulation alone, without switching to an oral antibacterial drug, to allow for proper assessment of both the efficacy and safety of the test drug. If two adequate and well-controlled trials are being conducted for the indication of CABP, it may be appropriate to allow oral switch in one of the trials, provided adequate safety data are available from other indications. If this approach is taken, the IV antibacterial should be administered for a minimum length of time (e.g., 72 to 96 hours) before switching to oral therapy. Objective criteria that allow for oral switch should be specified in the protocol and captured on the case report form. Clinical assessment should be performed at the time of IV to oral switch.

For drugs that have both an IV and oral formulation, appropriate criteria that allow for IV to oral switch should be specified in the protocol. The pharmacokinetics of the oral formulation should have been adequately evaluated to ensure comparable exposure and to determine an appropriate dosing regimen. These criteria should be listed on the case report form. If practice patterns allow, it may be appropriate to enroll hospitalized CABP patients in oral antibacterial trials.

[17] See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (http://www.fda.gov/cder/guidance/index.htm).

Currently, we do not recognize any surrogate markers as a substitute for clinical outcomes in CABP trials. Sponsors who wish to propose a surrogate marker for clinical outcome or the initial diagnosis of CABP should discuss this with the FDA early in the drug development process.

6. Safety Considerations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. All patients should be evaluated for safety at the time of each visit or assessment, regardless of whether the test drug has been discontinued. All adverse events should be followed until resolution, even if time on trial would otherwise have been completed.

A sufficient number of patients, including patients older than 65 years, should be studied at the dose and duration proposed for use to draw appropriate conclusions regarding drug safety. Safety evaluations and assessments should take into consideration the patient populations that are likely to be treated for CABP. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be needed based on the nonclinical and clinical profile of the specific drug under investigation. Longer term assessment of adverse events after discontinuation or completion of the antimicrobial should be considered, depending on the specific drug's potential for long-term or delayed adverse effects.

B. Specific Efficacy Trial Considerations

1. Trial Design

CABP trials should be randomized, double-blind, and active-controlled using a noninferiority or superiority design. Placebo-controlled trials are not appropriate for this indication.

2. Trial Population

The trial population should include patients 18 years of age and older with CABP. The trials should enroll patients with either confirmed CABP or with a high likelihood of CABP. An adequate number of patients with bacteriologically confirmed infections should be enrolled to allow assessment of the drug's effectiveness based upon the prespecified noninferiority margin, as described in section III.B.12., Statistical Considerations.

3. Inclusion and Exclusion Criteria

a. Clinical, radiographic, and microbiologic criteria

The diagnosis of CABP should be based on the following clinical, radiographic, and microbiologic criteria.

- **Clinical criteria.**
  - As part of the clinical picture of CABP, a patient should have at least three of the following symptoms and signs:
    - Cough with production of purulent sputum
    - Dyspnea or tachypnea
    - Chest pain
    - Fever, defined as body temperature greater than 38 degrees Celsius (100.4 degrees Fahrenheit) taken orally, greater than 38.5 degrees Celsius (101.2 degrees Fahrenheit) tympanically, or greater than 39 degrees Celsius (102.2 degrees Fahrenheit) rectally; or hypothermia (less than 35 degrees Celsius)[18]
    - Clinical findings of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)
  - Additional criteria that may support the diagnosis of CABP but not needed for inclusion are as follows:
    - Chills or rigors
    - Hypoxemia with a $PO_2 < 60$mm Hg while patient is breathing room air
    - An elevated total white blood cell count or leukopenia, or elevated immature neutrophils (bands)
  - We recommend using the Pneumonia Severity Index or Pneumonia Patient Outcomes Research Team (PORT) classification system for the purposes of enrollment and stratification.[19] The criteria that are used to calculate the PORT score and determine the risk class for each patient should be included in the case report form and in the datasets.
    - *IV antibacterials.* All patients being enrolled in IV antibacterial trials should have PORT scores of II or greater. No more than 25 percent of the enrolled population should have a PORT score of II and at least 25 percent of the population should have PORT scores of IV or greater.

[18] Some patients develop hypothermia, especially the elderly and others who have risk factors such as alcoholism, malnutrition, and other comorbid illnesses.

[19] Fine, MJ, TE Auble, DM Yealy et al., 1997, A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia, N Engl J Med, 336:243-50.

312 ▪ *Oral antibacterials.* Patients being enrolled in oral antibacterial trials should have
313 PORT scores of II or greater. At enrollment, at least 50 percent of these patients
314 should have PORT scores of III or greater.
315
316 • **Radiographic criteria.** The chest radiograph should show the presence of new
317 infiltrates in a lobar or multilobar distribution characteristic of bacterial pneumonia. The
318 final full report of the pretreatment and subsequent chest radiograph by the radiologist
319 should be included in the case report form.
320
321 • **Microbiologic criteria.** At the time of enrollment, an adequate specimen of respiratory
322 secretions should be obtained in all patients and sent to the laboratory for Gram stain,
323 culture, and in vitro antibacterial susceptibility testing performed on appropriate
324 organisms isolated from the specimen. Specimens should be processed according to
325 recognized methods.[20] Microscopic examination of Gram stained smears should be
326 performed. Specimens that have fewer than 10 squamous epithelial cells and more than
327 25 polymorphonuclear cells per low power field (100X magnification) are considered
328 appropriate for inclusion in evaluation of respiratory culture results. Ten to twenty fields
329 of the Gram stain smear also should be examined at 1000X magnification and the
330 morphology of potential pathogens recorded. The Gram stain should be performed and
331 the specimen plated for culture within 2 hours from the collection time, if the specimen is
332 kept at room temperature. Alternatively, these tests can be performed within 24 hours of
333 collection if the specimen is stored at 2 to 8 degrees Celsius before processing.
334
335 The specimen of respiratory secretions can be obtained by any of the following means:
336
337 – Deep expectoration
338 – Endotracheal aspiration in intubated patients
339 – Bronchoscopy with bronchoalveolar lavage or protected-brush sampling
340
341 All isolates considered to be possible pathogens should be saved in the event that
342 additional testing of an isolate is needed. For microbiological assessment, the
343 investigator should collect the following information:
344
345 – A description of how the sample was obtained, processed, and transported to the
346 laboratory.
347
348 – Identification of the bacterial isolate and serotype if *S. pneumoniae*.
349
350 – In vitro susceptibility testing of the isolates to both the study drug and other
351 antibacterials that may be used to treat CABP caused by the targeted pathogens. In
352 vitro susceptibility should be performed by using standardized methods unless

[20] American Society for Microbiology, 2007, Manual of Clinical Microbiology, 9th edition.

otherwise justified.[21] Sponsors should describe the exact methodology used for susceptibility testing if a standardized method was not used.

The following topics regarding detection of bacterial pathogens should be discussed with the FDA before trial initiation: 1) use of rapid diagnostic tests for bacterial pathogens (e.g., urinary antigen test for *S. pneumoniae*) or for respiratory viral pathogens; 2) microbiologic testing for bacterial pathogens associated with atypical pneumonia such as *L. pneumophila*, *M. pneumoniae*, or *C. pneumoniae*; and 3) use of biomarkers for detection of bacterial pathogens.

b. Exclusion criteria

Exclusion criteria include the following:

- Atypical pneumonia
- Viral pneumonia
- Aspiration pneumonia
- Hospital-acquired pneumonia, including ventilator-associated pneumonia
- Receipt of prior antibacterials (see section III.B.7., Prior Antibacterial Drug Use)
- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this does not exclude patients who have chronic obstructive pulmonary disease)
- Patients with primary or metastatic lung cancer
- Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis

4. Randomization, Stratification, and Blinding

Patients should be randomized to treatment groups at enrollment. All trials should be double-blind unless there is a compelling reason for unblinding.

We recommend stratification by age (e.g., younger than 50 years, 50 years of age or older) and PORT scores (as outlined for entry criteria in section III.B.3.a., Clinical, radiographic, and microbiologic criteria).

[21] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute.

5. Special Populations

The trials should include patients 18 years of age and older, of both sexes, and all races. If sponsors wish to pursue CABP trials in pediatric patients, they should discuss the development plans with the FDA. Patients with renal or hepatic impairment can be enrolled provided pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined.

6. Choice of Comparators

Placebo-controlled trials are not appropriate for this indication. The active comparator should be an FDA-approved antibacterial that is considered standard of care for this indication (e.g., guidelines published by professional societies) at the recommended dosage.

7. Prior Antibacterial Drug Use

The use of prior antibacterial drugs effective against bacteria that cause CABP should be avoided in a noninferiority trial (except as described below) because such treatments will reduce the difference between treatment arms and allow an incorrect conclusion of noninferiority. However, patients who have received prior antibacterial therapy and who are considered clinical failures can be enrolled provided objective criteria for treatment failure are prespecified and documented on the case report form. Also, patients can be enrolled if they have received prior antibacterial therapy that lacks in vitro activity against the baseline pathogen.

8. Concomitant Medications

Concomitant antibacterial therapy for other infections should not be allowed during the trial until after the test-of-cure visit. Patients who receive such therapy should be excluded from the evaluable population and will be considered failures in the intent-to-treat (ITT) and the modified intent-to-treat (MITT) populations. Patients requiring rescue antibacterial therapy should be considered treatment failures and should be included in the ITT, MITT, and per-protocol populations.

9. Efficacy Endpoints

a. Primary endpoints

The following primary endpoints can be considered for CABP trials.

- **Primary clinical outcome based on complete resolution of signs and symptoms measured at a fixed time point**
  - *Clinical success.* A patient who is alive and has resolution of disease-specific signs and symptoms present at enrollment and who has no new symptoms or complications attributable to CABP is defined as a clinical success.[22]

[22] Some patients may have a prolonged cough despite resolution of other signs and symptoms of CABP. Such patients can be considered clinical successes provided they are not given additional antibacterials and are followed until resolution of the cough.

- *Clinical failure.* Patients designated as clinical failures at an early time point should be designated as clinical failures for all subsequent follow-up visits. Clinical failure is defined as follows:
  - All-cause mortality within 30 days of start of study drug
  - Lack of resolution of baseline CABP-specific signs and symptoms at the test-of-cure visit
  - Progression or development of new symptoms or radiologic findings attributable to CABP at any time point after enrollment
  - Development of complications of CABP such as empyema or lung abscess
  - Need for rescue therapy with nonstudy antibacterial drugs

- **Primary clinical outcome based on time to resolution of signs and symptoms**

  Currently, endpoints based on time to resolution of signs and symptoms are only applicable to superiority trials because an appropriate noninferiority margin has not been defined. If a patient-reported outcome (PRO) tool is used, its content validity and other measurement properties should be demonstrated in the population represented in the clinical trial. Relevant details regarding the planned trial design, analysis, and interpretation of the PRO findings should be discussed with the FDA before trial initiation.

b. Secondary endpoints

Sponsors can present secondary analyses on endpoints such as time to resolution of signs and symptoms (where the primary endpoint is complete resolution) or other endpoints of interest.

Sponsors should be aware that analyses of secondary and additional endpoints usually will be considered exploratory, because trials usually are not designed to address the multiplicity questions raised by these analyses. It is possible, however, to identify in the statistical analysis plan particular analyses and subsets of interest when the trial is successful on its primary endpoint, and, using sequential approaches or multiplicity corrections, reach statistically valid conclusions on secondary endpoints. Analyses of secondary and additional endpoints is often most helpful for identifying areas for study in future trials.

c. Patient-reported outcome instruments

A PRO instrument can be used to measure patient symptoms and self-reported signs. If a PRO instrument is used for measuring responses that will be based on a scaled score, then the score rather than an endpoint of complete symptom resolution should be used as the outcome variable. An outcome scale can be used for describing categorical responses (e.g., *success*, *improvement*, and *failure*) at each time point if the criteria for the categories have been well-developed and

validated. If an alternative to a PRO is used, the method of assessment should be a well-defined and reliable method of assessing patient response. Any tool used to assess time to resolution of signs and symptoms should be discussed with the FDA before trial initiation.

Because no PRO instrument has been recognized by the FDA for this indication, exploratory testing of a well-developed PRO instrument in clinical trials may justify its use to support primary or secondary study objectives in subsequent trials. Development of the new instrument should begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol. If the PRO tool is not developed for assessment of the primary endpoint, it may be appropriate to evaluate its use for assessment of secondary endpoints.

For more information regarding the development of such outcome measures, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.[23]

10. Trial Visits and Timing of Assessments

a. Entry visit

At the entry visit, the following information should be captured and recorded on the case report form:

- History and physical examination
- Baseline signs and symptoms including vital signs
- Chest X ray
- PORT score criteria and calculation
- Microbiologic specimens: adequate sputum specimens as determined by Gram stain (see section III.B.3.a., Clinical, radiographic, and microbiologic criteria), sputum culture, blood cultures, other rapid diagnostic tests
- Laboratory tests: hematology, chemistry, and others as appropriate

b. On-therapy visits

Each patient should have on-therapy assessments of signs and symptoms. The frequency of these visits depends on whether the endpoint is assessed at a fixed time point or a time-to-resolution endpoint is used. The ability to detect differences between study therapies for a time-to-resolution endpoint may be increased if assessments are done more often. These assessments

[23] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

can be performed by the investigator during a visit to the investigator's office or by a validated PRO instrument. Patients should be clinically evaluated by the investigator at a 48- to 72-hour visit to ensure that there is no clinical worsening at this time.

Assigning clinical failure and permitting use of rescue antibacterial therapy should be reserved for patients who are worsening or not improving on their assigned treatment arm; specific criteria to initiate rescue therapy in these patients should be included in the protocol. Appropriate specimens for microbiologic evaluation should be obtained in these patients before instituting the new antibacterial therapy. It is important that investigators distinguish between patients who are worsening or not improving (i.e., where antibacterial rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy and thereby achieve clinical success. In the case of clinical failure, therapy should be changed to an appropriate alternative antibacterial treatment for CABP, with other therapeutic modifications as necessary. Patients who receive rescue therapy should continue to have protocol-specified assessments identical to patients who continue to receive their originally assigned treatment and will be considered treatment failures in both complete resolution and time to resolution endpoints.

Investigators should document findings from on-therapy office visits (e.g., history, physical examination, and laboratory test results) on the patient case report form. If the investigator contacts the patient by telephone or by another interactive technology, documentation of the specific questions asked, how they were asked, and the responses given should be captured on the case report form. If a validated diary is used to capture patient symptoms during this trial, this information should also be recorded on the patient case report form.

c. End-of-therapy visit

Patients should be evaluated clinically at the end of the prescribed therapy. Laboratory assessments for safety should be performed at this visit. If the study drug needs to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol. Patients without clinical improvement or with progression of signs and symptoms should be considered failures and alternative antibacterial rescue therapy should be provided.

d. Test-of-cure visit

The test-of-cure visit should occur after completion of study drug at a time when the drug is expected to have cleared from the infection site. The test-of-cure visit should occur at a fixed time point relative to randomization (5 to 10 days after completing therapy). If the treatment durations in the test and control arms are different, the timing should be based on the longest treatment duration. For drugs with long half-lives, sponsors should discuss the timing of the visits with the FDA during protocol development. At this visit, the investigator should obtain medical history including adverse events, perform physical examination, and obtain appropriate laboratory and radiological measurements.

e. Follow-up assessment

The follow-up assessment should occur approximately 1 to 2 weeks after the test-of-cure visit. This assessment can be performed by a telephone contact with patients who were considered to be clinical successes and had no adverse events noted at the test-of-cure visit. For patients with adverse events occurring at or after the test-of-cure visit, investigators should perform an assessment that includes a medical history, a physical examination, appropriate laboratory evaluations, and identification of any new adverse events. All adverse events should be followed to resolution. It is important that all patients are followed for at least 30 days after enrollment to capture the 30-day mortality data.

11. Endpoint Adjudication

Generally in CABP trials, there is no need for endpoint adjudication. If a sponsor believes that adjudication or endpoint assessment committee is necessary, this should be discussed with the FDA before trial initiation.

12. Statistical Considerations

The trial hypotheses and the analysis methods should be stated in the protocol and/or the statistical analysis plan, and should be finalized before trial initiation. Changes in statistical analysis plans made later may be appropriate if made entirely blindly; however, documenting unequivocal maintenance of the blind can prove difficult. The trials should be adequately powered to detect differences between treatment arms if differences exist. If sponsors choose to test multiple hypotheses, they should address issues related to the potential inflation of false positive results (overall type I error rate) because of multiple comparisons. These issues should be discussed with the FDA during protocol development, and if any subsequent changes are considered they should be discussed with the FDA before incorporation into the statistical analysis plan.[24]

a. Analysis populations

The following definitions apply to various analysis populations in CABP clinical trials:

- Safety population — All patients who received at least one dose of drug during the trial.

- ITT population — All patients who were randomized.

- MITT population (also sometimes referred to as microbiological intent-to-treat population) — All randomized patients who have a baseline bacterial pathogen known to cause CABP against which the test drug has antibacterial activity. This includes bacterial pathogens identified in blood, appropriate sputum specimen, or other test such as urinary antigen test. Patients should not be excluded from this population based upon events that occur postrandomization (e.g., loss to follow-up).

[24] See ICH E9 and ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

- Clinically evaluable or per-protocol populations — Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.

- Microbiologically evaluable populations — Patients who meet the definition for the MITT population and who follow important components of the trial as specified in the protocol.

Generally, ITT analyses are preferred for superiority trials, although use of the MITT population may greatly increase the chance of demonstrating effectiveness by excluding patients who do not have the disease under study. Although the ITT population is usually the primary analysis in a difference-showing trial, the inherent bias toward the null in noninferiority trials poses a significant problem, and in this case ITT may not be the preferred analysis.[25] Particularly where the noninferiority margin is based primarily on microbiologically defined patients, the MITT population is preferred. Moreover, for similar reasons, the microbiologically evaluable population should be strongly considered. In addition, consistency of results should be evaluated in the ITT and clinically evaluable populations.

b. Noninferiority margins

Based on a review of the historical data, we believe that noninferiority trials are appropriate for the CABP indication (see Appendix). This issue was discussed at the Anti-Infective Drugs Advisory Committee meeting in April 2008. The noninferiority margins can be justified based on historical evidence of the treatment effect of antibacterial therapy on mortality in patients with lobar or pneumococcal pneumonia. Sponsors should justify the noninferiority margin for the proposed trial design and population enrolled. In the final trial report, sponsors should address issues relating to the noninferiority margin as it applies to the trial population.

For drugs with an IV formulation, the MITT population will be considered as the primary analysis population and a 15 percent noninferiority margin is appropriate. However, as outlined in section III.B.3., Inclusion and Exclusion Criteria, no more than 25 percent of patients enrolled should have PORT scores of II and a minimum of 25 percent of patients should have a PORT score of IV or greater.

For drugs with only an oral formulation, the MITT population will be considered as the primary analysis population and a 10 percent noninferiority margin is appropriate. As outlined in section III.B.3., Inclusion and Exclusion Criteria, patients with a PORT score of I should be excluded and at least 50 percent of the population should have a PORT score of III or greater.

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate,

[25] See ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

the noninferiority margin (for a noninferiority trial), or the amount by which the study drug is expected to be superior (for a superiority trial). The appropriate sample size should be estimated using a two-sided α=0.05.

d. Missing data

There is no single optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. Analyses that exclude patients are subgroup analyses, and patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways. The method of how missing data will be handled should be specified in the protocol. Sponsors also should present sensitivity analyses such as including all missing patients as failures or including all missing patients as successes. Interpretation of trial results may be affected if the rates of missing data are different across treatment arms.

e. Interim analyses and data monitoring committee

If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate (if any). It is important that the interim analysis not affect trial conduct and thereby compromise trial results. This can be accomplished by creating an independent data monitoring committee (DMC). Such a committee also might be created if there were safety concerns about the drug or the treatment approach. If a DMC is used, a detailed charter with the composition of the committee members, decision rules, details on the measures taken to protect the integrity of the trial, and the standard operating procedures should be provided for review.[26]

f. Other analyses of interest and secondary endpoints

Sponsors can present secondary analyses on other endpoints of interest such as:

- Mortality and clinical response in bacteremic versus nonbacteremic patients
- Response at earlier time points or at the end of therapy
- Response based on patient demographics such as age, geographic region, underlying renal impairment, and microbiologic etiology

g. Statistical analysis plan

Before initiation of any phase 3 CABP trial, sponsors should provide a detailed statistical analysis plan to the FDA.

[26] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (http://www.fda.gov/cder/guidance/index.htm).

13. Risk-Benefit Considerations

Risk-benefit considerations depend on the population being studied and the safety profile of the drug being investigated.

C. Other Considerations

1. Labeling Considerations

The labeled indication will be community-acquired bacterial pneumonia caused by the specific bacteria identified in patients in the clinical trials and will reflect the patient population enrolled in the clinical trials.

2. Antimicrobial Resistance Claims

To obtain a claim for resistant pathogens in CABP, the claim should be relevant to CABP and sponsors should present data from their clinical trials to demonstrate treatment effect with the drug against resistant organisms. Sponsors seeking resistance claims for CABP are encouraged to contact the review division regarding appropriate trial designs for resistant pathogens and to discuss the desired resistance claims.

APPENDIX: NONINFERIORITY MARGIN JUSTIFICATION FOR CABP

Background

Conceptually, the selection of a noninferiority margin is a two-step process. The first step involves reliable estimation of the treatment effect of the active comparator (i.e., effect of the active comparator over placebo, referred to as M1) based upon placebo-controlled trials. When data from placebo-controlled trials are not available, an alternative means to estimate treatment effect is to use available data from trials of treated versus untreated disease, remaining conscious of the risks of cross-study comparisons. All use of such historical estimates of treatment effect relies on the *constancy* assumption, the assumption that the past effect of the active control is the effect it will have in the contemporary noninferiority trial. For example, if the present effect is in doubt because of changes in ancillary therapy, it may be necessary to *discount* the historically based estimate of the control effect. The estimate of M1 includes any such discounting. The second step involves clinical judgment regarding how much of the estimated treatment effect (M1) should be preserved in determining a clinically acceptable noninferiority margin, referred to as M2.

Because no data from placebo-controlled trials in CAP are available, we reviewed results from historical comparative clinical trials of treated versus untreated controls and from observational studies that evaluated mortality in patients treated with antibacterial drugs or with no specific therapy to estimate the treatment effect of antibacterial drugs in CAP. Based on review of these data, we believe that noninferiority trials are appropriate for the specific indication of CABP, as described in this guidance. Historical studies and clinical trials of antibacterial treatment of pneumonia provide evidence that antibacterial drugs reduced mortality in patients with pneumococcal or lobar pneumonia. Although the treatment effect varied across studies and clinical trials, the effect of treatment on survival was consistently greater in older patients (older than 50 years) and in patients with bacteremia.

Direct extrapolation of treatment effect from historical studies and clinical trials to contemporary CABP clinical trials is difficult. The historical-controlled clinical trials lacked blinding and randomization as currently defined. There is also considerable uncertainty regarding the similarity of patient populations from historical studies and clinical trials to populations in current clinical trials. For example, patients today may have different comorbidities and risk factors for pneumonia, or may have received pneumococcal vaccine. Additionally, improved standards of medical care today may result in improved outcomes (e.g., care in an intensive care unit, mechanical ventilation, hemodynamic support).

Another area of uncertainty in extrapolating the treatment effect of antibacterial drugs from historical studies and clinical trials is the spectrum of bacterial pathogens that cause CABP today in comparison to the early mid-twentieth century. In most of the historical studies and historical-controlled clinical trials, CAP was considered synonymous with pneumococcal pneumonia, whereas in recent CAP clinical trials, less than 20 percent of patients enrolled had documented *S. pneumoniae*.[27] Although *S. pneumoniae* remains the most common cause of CAP, we know that

[27] Higgins, K, M Singer, T Valappil, S Nambiar, D Lin, and E Cox, 2008, Overview of Recent Studies of Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3) S150-S156.

CAP also can be caused by other pathogens such as *H. influenzae* or *parainfluenzae*, *S. aureus*, and *M. catarrhalis*; atypical bacteria such as *M. pneumoniae* and *C. pneumoniae*; and *Legionella* species, as well as respiratory viruses. Limited information is available on antibacterial treatment effect in CAP caused by *M. pneumoniae*, whereas for pathogens such as *C. pneumoniae*, the size of the treatment effect remains unknown.

Most of the historical studies and clinical trials reported mortality as the clinical outcome. Mortality has not been used as a primary endpoint in recent CAP clinical trials, although it has been a part of the composite endpoint of clinical failure. For noninferiority trials, extrapolating quantitative estimates of treatment benefit from a mortality endpoint to a clinical failure endpoint raises questions regarding the applicability of the treatment effect for mortality to other outcome measures. In current clinical trials, patients who are not improving on therapy would be considered clinical failures, and alternative antibacterial treatment (i.e., rescue therapy) would be initiated before death occurs. The endpoint of clinical failure in a present-day clinical trial includes patients who would have progressed to death in a historical study or clinical trial, but it may include others who ultimately would not have died. Thus, it appears reasonable to include in current trials death, disease progression, and lack of clinical improvement as an appropriate endpoint that reasonably well reflects past effects on mortality.

Although some of the historical studies and clinical trials attempted to grade severity of illness, descriptions of how severity was assessed were limited. The PORT score, which classifies patients by prognosis (risk of mortality) based on age and other criteria, is used for clinical decision making regarding hospitalization. Current treatment guidelines recommend hospitalization of patients who have a PORT score of III or greater.[28] The PORT score is weighted heavily by age, and the majority of patients with PORT scores of III or greater will be over 50, have significant comorbidities, or have severe physiologic derangements upon presentation.

Historical studies and trials

Observational

In several observational studies of pneumococcal pneumonia, a significant mortality benefit was shown among patients treated with antibacterial drugs compared to patients who received no specific therapy (untreated), as summarized in Table A1.

[28] Fine, MJ, TE Auble, DM Yealy, BH Hanusa, LA Weissfeld, DE Singer, CM Coley, TJ Marrie, and WN Kapoor, 1997, A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia, N Engl J Med, 336:243-50.

Table A1. Mortality in Observational Studies of Pneumococcal Pneumonia[1]

Publication	Population	Mortality (%) Untreated N (Study Years)	Mortality (%) Antibacterial-Treated	Treatment Difference Untreated-Treated (95% Confidence Interval)
Finland (1943)[2]	≥ 12 years old bacteremic and nonbacteremic	N=2,832 (1929-1940)* 41%	N=1,220 (1939-1941) 17% (sulfonamides)	24% (21,27)
Dowling and Lepper (1951)[3]	≥ 10 years old bacteremic and nonbacteremic	N=1,087 (1939, 1940)* 30.5%	N=1,274 (1938-1950) 12.3% (sulfonamides) N=920 (1938-1950) 5.1% (penicillins and tetracyclines)	18.5% (15,21) 25.4% (22,28)
Austrian and Gold (1964)[4]	≥ 12 years old bacteremic	N=17 (1952-1962) 82%	N=437 (1952-1962) 17%	65% (41,79)

[1] Singer, M, S Nambiar, T Valappil, K Higgins, and S Gitterman, 2008, Historical and Regulatory Perspectives on the Treatment Effect of Antibacterial Drugs for Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3): S216-S224.
[2] Finland, M, 1943, Chemotherapy in the Bacteremia, Conn State Med J, 7:92-100.
[3] Dowling, HG and MH Lepper, 1951, The Effect of Antibiotics (Penicillin, Aureomycin and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with other Methods of Therapy, AM J Med Sci, 222:396-402.
[4] Austrian, R and J Gold, 1964, Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia, Ann Intern Med, 60:759-776.
* Historical controls

Despite the many limitations of these historical studies, such as observational study design and use of historical controls, the mortality benefit demonstrated with antibacterials was substantial. The lower limit of the 95 percent confidence interval (CI) for the treatment difference (antibacterials minus placebo) from the Finland study was 21 percent. In the Dowling and Lepper study, the lower limit of the 95 percent CI for the treatment difference (antibacterials minus placebo) was 15 and 22 percent for patients who received sulfonamides or penicillins and tetracyclines respectively; the latter group seems more likely to reflect the effect of modern antibacterial treatments. In the Austrian and Gold study, which only evaluated patients with bacteremic pneumococcal pneumonia, the lower limit of the 95 percent CI was 41 percent. In these studies of pneumococcal pneumonia, the mortality difference between antibacterial-treated and untreated groups was largest in patients older than 50 years, in patients treated with penicillin or tetracyclines rather than sulfonamides, and in patients with pneumococcal bacteremia.

The mortality associated with pneumonia is greatest at the extremes of age. Persons over the age of 50 years exhibit the greatest mortality, and correspondingly antibacterial therapy has its

greatest effect in reducing mortality in these populations. This observation is apparent from looking at the data from Dowling and Lepper in patients with pneumococcal pneumonia, as shown in Table A2.

Table A2. Mortality By Age from Dowling and Lepper (1951)[1]

Age (Years)	Untreated		Sulfa-Treated		Penicillin, Tetracycline-Treated		Serum-Treated	
	N	Deaths (%)	N	Deaths (%)	N	Deaths (%)	N	Deaths (%)
10 to 49	725	139 (19.2)	988	79 (8.0)	684	18 (2.6)	710	74 (10.4)
50 to > 70	362	192 (53.0)	286	78 (27.3)	236	20 (12.3)	179	76 (42.5)
Total	1,087	331 (30.5)	1,274	157 (12.3)	920	47 (5.1)	889	150 (16.9)

[1] Dowling, HG and MH Lepper, 1951, The Effect of Antibiotics (Penicillin, Aureomycin and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with other Methods of Therapy, AM J Med Sci, 222:396-402.

As shown in Table A3, an approximate doubling of the size of the treatment effect with antibacterial drugs is noted in patients older than 50 years compared to patients younger than 50 years.

Table A3. Treatment Difference By Age in Patients with Pneumococcal Pneumonia from Dowling and Lepper (1951)[1]

Treatment	Age	Treatment Difference (% Death Untreated- % Death Treated)
Sulfa	< 50	11.2 (7.8, 14.5)
	≥ 50	25.8 (18.5, 33.1)
Penicillin, tetracycline	< 50	16.5 (13.4, 19.6)
	≥ 50	44.6 (38.3, 50.8)
Serum	< 50	8.7 (5.1, 12.4)
	≥ 50	10.6 (1.7, 19.5)

[1] Dowling, HG and MH Lepper, 1951, The Effect of Antibiotics (Penicillin, Aureomycin and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with other Methods of Therapy, AM J Med Sci, 222:396-402.

Controlled trials

In the historical-controlled clinical trials in patients with lobar pneumonia, the point estimates for the treatment difference for mortality in patients treated with sulfapyridine or no specific therapy varied from 10 to 19 percent for all ages combined, as shown in Table A4. The CI for each of the trials (or subtrials) are wide, as the number of patients enrolled in most of these trials was small. A high proportion of the population in these trials was younger than 50 years of age, a group in which the treatment effect was smaller in the observational studies. The numbers of patients in these trials was not sufficient to provide informative estimates of the effect of age on mortality.

Table A4. Mortality in Historical-Controlled Trials of Lobar Pneumonia[1]

Publication	Population	Mortality (%) Untreated N	Mortality (%) Antibacterial-Treated	Treatment Difference Untreated-Treated (95% Confidence Interval)
Evans and Gaisford (1938)[2]	8-68 years old, 86% < 50 years old; specific serotypes identified in 22%, bacteriology in remainder not described	27/100 (27%)	8/100 (8%)	19% (8.8, 29.2)
Graham (1938)[3]	86% had pneumococcal pneumonia, 29% bacteremic, 70% < 50 years old	7/30 (23%)	3/50 (6%)	17% (0.1-36.4)
Agranat (Europeans substudy, 1938)[4]	97% < 50 years old, frequency of bacteremia not reported	6/27 (22%)	2/22 (7%)	15% (-6.2, 35.5)
Agranat (Non-Europeans substudy, 1938)[4]	81% < 50 years old, frequency of bacteremia not reported	16/86 (19%)	6/71 (9%)	10% (-0.3, 20.6)

[1] Singer, M, S Nambiar, T Valappil, K Higgins, and S Gitterman, 2008, Historical and Regulatory Perspectives on the Treatment Effect of Antibacterial Drugs for Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3): S216-S224.

[2] Evans, GM and WF Gaisford, 1938, Treatment of Pneumonia with 2-(aminobenzenesulphonamido) pyridine, Lancet, 2:14-19.

[3] Graham, D, WP Warner, JA Dauphinee, and RC Dickson, 1939, The Treatment of Pneumococcal Pneumonia with Dagenan (M. & B. 693), Can Med Assoc J, 40:325-332.

[4] Agranat, AL, AO Dreosti, and D Ordman, 1939, Treatment of Pneumonia with 2-(aminobenzenesulphonamido) pyridine (M. & B. 693), Lancet, 1:309-317.

Estimation of M1

The estimate of the treatment effect should take into consideration several sources of uncertainty while relying upon the data from previously conducted studies and clinical trials as discussed below:

- The first source of uncertainty is the precision of the estimate of the treatment effect from the historical data. The 95 percent CIs have been used to estimate the range within which the true treatment effect is likely to fall.

- The second source of uncertainty arises from the issue of whether the magnitude of the treatment effect that was observed in previously conducted studies and clinical trials will be different from that which would be seen in a future clinical trial (i.e., constancy assumption).

- The third source of uncertainty is type I error (concluding that the test drug is noninferior when it is not). The issue of type I error in a present-day CABP trial is controlled through choosing an alpha of two-sided 0.05 (i.e., one-sided 0.025) as a means to control for alpha error.

Acknowledging the uncertainties inherent in the historical data, an estimate of the treatment effect from the observational studies, based on the lower bound of the 95 percent CI, is 22 percent for penicillins and tetracycline in patients with pneumococcal pneumonia and 15 percent for sulfa drugs in treating pneumococcal pneumonia. For the three controlled trials, we performed a meta-analysis using a random effects model to control for intratrial variability. The point estimate for the treatment difference and the corresponding 95 percent CI was 15.1 percent (8.8 percent, 21.4 percent). Several factors should be considered in interpreting the lower bound of 8.8 percent derived from this meta-analysis when estimating the treatment effect for a present-day CABP trial with designs as described in this guidance.

This estimate of the treatment effect may be an underestimate for the following reasons:

- The vast majority (at least 70 percent) of patients in the controlled trials were younger than 50 years of age. Based on data from observational studies in pneumococcal pneumonia, it is evident that mortality increases with age and the treatment effect in patients 50 years of age and older is much larger than that seen in patients younger than 50 years of age. The design for present-day CABP trials as described in this guidance will enroll patients with a set distribution of PORT scores and hence enroll an adequate number of patients 50 years of age or older.

- All patients in the controlled trials were treated with oral sulfonamides, which were dosed sub-optimally in some patients in at least two of the trials in Table A2. In the observational studies of pneumococcal pneumonia, the treatment effect based on mortality was greater with penicillins than with sulfonamides (see Table A1). For a present-day CABP trial, the treatment effect is likely to be larger considering that more effective therapies and optimal dosage regimens are used in the clinical trials.

- The treatment effect for an endpoint such as clinical failure would likely be larger than that seen with a mortality endpoint. It is reasonable to assume that some of the patients in present-day trials would progress to death in the absence of rescue therapy. If the definition of clinical failure (including death) were applied to a historically conducted study or clinical trial, the clinical failure endpoint would be at least as great as the observed mortality. Thus, the treatment effect based on mortality in historical studies or clinical trials can be extrapolated to a composite endpoint in a present-day trial that includes both mortality and clinical failure. It is important to note that any differential

effect on mortality should be assessed independent of its inclusion in the composite endpoint.

This estimate of the treatment effect may be an overestimate for the following reasons:

- Predominance of data in the historical studies and clinical trials was derived from patients with pneumococcal disease compared to the mixture of microbial etiologies that would likely be present in a present-day CABP trial.

- Advances in supportive care such as mechanical ventilation, blood pressure support, and other intensive care interventions may reduce the mortality observed in a present-day trial compared to what was seen in the 1930s and 1940s.

- The general health status of patients may be somewhat better in a present-day CABP trial. Factors such as improved nutritional status, use of pneumococcal vaccine, underlying comorbidities such as diabetes, or immunocompromise may affect the outcome of pneumococcal disease.

Contemporary CAP clinical trials

In a review of previously conducted clinical trials of oral antibacterial drugs for CAP the median and mean ages were 45 and 46 years of age, respectively.[29] Ninety to ninety-five percent of patients in these CAP trials had PORT scores of I or II and 5 to 10 percent had a PORT score of III. In trials of intravenous drugs for CAP, enrolled patients were somewhat older with a mean age of 56 years; the corresponding PORT scores for these trials were 55 percent PORT I or II, 20 percent PORT III, 20 percent PORT IV, and less than 5 percent PORT V.

Because of the differences in historical studies and clinical trials and present-day CAP trials, we also examined data from a more recent daptomycin trial that provide some insight into the treatment effect of antibacterial drugs in CAP.[30] We present some analyses discussed in the paper and discuss results of additional analyses performed by the FDA.

Two clinical trials were conducted comparing daptomycin to ceftriaxone in the treatment of patients with CAP caused by Gram-positive organisms. The second trial was terminated early based on failure of the first trial to demonstrate noninferiority. Data presented are aggregate data from the two trials. The data provide useful information on the questions of the effect of prior antimicrobial therapy on treatment outcomes and whether these effects vary by PORT score. The mean age was 55 years and the distribution of PORT scores was approximately 42 percent PORT II, 30 percent PORT III, and 28 percent PORT IV.

[29] Higgins, K, M Singer, T Valappil, S Nambiar, D Lin, and E Cox, 2008, Overview of Recent Studies of Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3) S150-S156.

[30] Pertel, PE, P Bernardo, C Fogarty et al., 2008, Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia, Clin Infect Dis, 46:1142-51.

In these trials, prior antibacterial therapy was defined as any potentially effective antibacterial drug received within 72 hours of starting study drug. Patients were excluded if they had received potentially effective antibacterial therapy for more than 24 hours within 72 hours of enrollment. In the published post-hoc analysis of these trials, prior effective therapy was defined as antibacterial drugs with both greater potency and longer half-lives (such as levofloxacin, ceftriaxone, azithromycin, and clarithromycin). Patients who had received no antibacterial drugs or only drugs with lesser potency or shorter half-lives (such as penicillins, tetracyclines, or trimethoprim-sulfamethoxazole) were classified as having received no prior effective therapy.

As shown in Table A5, in subgroup analyses in the clinically evaluable population of the aggregated daptomycin CAP trials, it appears that prior antibacterial therapy of 24 hours or less duration within the 72-hour period before enrollment has an effect on clinical response and could lessen the treatment effect that an experimental drug could demonstrate. Prior antibacterial therapy had a greater effect on the cure rates in the daptomycin arm compared to the ceftriaxone arm. Similar results were seen in the ITT and MITT populations. Although these are post hoc analyses of subgroups from the aggregate trial data, they suggest the importance of limiting or avoiding prior antibacterial therapy and that prior antibacterial therapy may reduce the treatment effect of an antibacterial drug under study.

Table A5. Effect of Prior Antibacterial Therapy on Clinical Response By Treatment Arm (Clinically Evaluable Populations)[1]

Clinical Response	Prior Antibacterial Therapy		Treatment Difference (95% Confidence Interval)	No Prior Antibacterial Therapy		Treatment Difference (95%Confidence Interval)
	Daptomycin N=97 n (%)	Ceftriaxone N=92 n (%)		Daptomycin N=272 n (%)	Ceftriaxone N=279 n	
Cure rate	88 (90.7)	81 (88)	2.7 (-6.1%, 11.5%)	205 (75.4)	245 (87.8)	-12.4% (-18.8, -6.0)

[1] Pertel, PE, P Bernardo, C Fogarty et al., 2008, Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia, Clin Infect Dis, 46:1142-51.

The question of whether patients with higher PORT scores are less likely to show an effect of prior antibacterial therapy than patients with lower PORT scores was also explored. For example, in more severely ill patients, do 24 hours or less of prior antibacterial therapy affect clinical response? Analyses of the daptomycin trials revealed that prior antibacterial therapy affects the observed treatment effect even in patients with PORT scores of III or IV.

Future CABP trials

Patient population

This guidance recommends inclusion and exclusion criteria (section III.B.3.) designed to enroll patients with CAP of a bacterial etiology (i.e., CABP) with a set distribution of PORT scores.

This increases the likelihood that the patient population in CABP trials is comparable to that studied historically (pneumococcal or lobar pneumonia).

Age

Age is a strong predictor of mortality in CAP, and from the historical studies and clinical trials of patients with pneumococcal pneumonia there was a larger treatment effect in patients older than 50 years of age. As noted in Table A3, the point estimate for treatment effect approximately doubles in the patient population older than 50 years of age compared to the population younger than 50 years of age. Age is also a large factor in the PORT score, and specifying a population with this distribution of PORT scores as outlined in the guidance will lead to enrollment of a population that is largely older than 50 years of age. Based on these factors, we anticipate the following:

- For an IV drug trial, approximately 75 percent of the population will be 50 years of age or older
- For an oral drug trial, approximately 50 percent of the population will be 50 years of age or older

Thus, CABP trials as described in this guidance should enroll a patient population with lobar disease on chest X ray along with other cardinal signs of pneumonia, a population with the aforementioned distribution of PORT scores, and an age distribution of approximately 75 percent (in IV drug trials) or 50 percent (in oral drug trials) older than 50 years of age.

Comparator agents

Present-day CABP trials should use comparator agents that are FDA-approved for CAP and that are recommended by guidelines to achieve a comparator with a high degree of efficacy. Based upon the finding that prior antimicrobial therapy affected the cure rates in the daptomycin trials, it is critical that the use of prior antibacterial therapy be minimized in the present-day CABP trials. Drug trials for CABP should exclude patients who have received any prior antibacterial therapy.

Most of the available data on treatment effect are data from many years ago and there have been advances in medical care over this time period. Nevertheless, this information provides evidence of treatment effect with antibacterials and allows for reasonable judgments regarding expected treatment effect in a present-day CABP trial. The patient characteristics and trial design factors that are described above are chosen to design a trial that has the capacity to achieve an expected treatment effect.

Noninferiority margin

IV antibacterial drugs

In a patient population enrolled in a present-day CABP trial for an IV formulation as described in this guidance, the treatment effect is likely to exceed that which was observed for the trials described in Table A4 with a lower bound of 8.8 percent, because of: 1) the inclusion criteria; 2) the distribution of PORT scores; 3) the proportion of patients older than 50 years of age; 4) the exclusion of patients with prior antibacterial therapy; and 5) the use of an approved and guideline-recommended comparator antibacterial therapy. The observation that the lower bounds of the 95 percent CI for the treatment effect varied from 15 to 22 percent in the observational studies in patients with pneumococcal pneumonia (Table A1) suggests that there is a larger treatment effect when a bacteriologic diagnosis is made.

The MITT population will be considered the primary analysis population. Use of the MITT population provides reasonable assurance that most of the patients in the trial have a documented microbiologic diagnosis. Thus, based on the evidence discussed in this Appendix, a reasonable estimate of M1 for the MITT population for the endpoint of clinical outcome in a CABP trial is at least 15 percent for patients enrolled in IV antibacterial trials and an M2 of up to 15 percent is considered appropriate in the MITT population.

Oral antibacterial drugs

Oral antibacterial drug trials generally enroll patients with less severe disease than IV antibacterial drug trials, introducing additional uncertainly regarding the antibacterial treatment effect. As described above, the MITT population will be considered the primary analysis population. Use of the MITT population provides reasonable assurance that most of the patients in the trial have a documented microbiologic diagnosis.

In oral antibacterial drug trials, there are greater uncertainties in the treatment effect. Because patients enrolled in such trials can have illness of lesser severity, the magnitude of treatment effect may be smaller. Thus, based on the evidence discussed in this Appendix, a reasonable estimate of M1 for the MITT population for the endpoint of clinical outcome in a CABP trial of oral antibacterial drug is at least 10 percent and an M2 of up to 10 percent is considered appropriate for the MITT population.

For both IV and oral antibacterial drug trials, results in the ITT, clinically evaluable, and microbiologically evaluable populations should be examined for consistency with the results in the MITT population.

Summary

Based on data from historical studies and clinical trials, appropriate noninferiority margins for CABP trials for IV drugs and oral drugs have been described. To arrive at these margins from the available data a series of judgments were required. In addition, the recommended design of

1093 the CABP trials includes a number of provisions to select and evaluate populations that are
1094 appropriate for the proposed margins. These provisions include defining CABP as a clinical
1095 syndrome consistent with bacterial pneumonia and limiting enrollment to an appropriate patient
1096 population based on age, severity of illness, making the MITT the primary analysis population,
1097 and excluding patients who received prior antibacterial therapy.

Selected References for the CABP Background Document:

1. Mandell LA, Wunderink RG, Anzueto A, et. al., 2007. Infectious Disease Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis; 44: S27-72.

2. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis 2010;50:202-209.

3. Østergaard L, Andersen PL. Etiology of community-acquired pneumonia: evaluation by transtracheal aspiration, blood culture, or serology. Chest 1993;104:1400-1407.

4. Ruiz-González A, Falguera M, Nogués A, Rubio-Caballero M. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. Am J Med. 1999 Apr;106(4):385-90.

5. Pertel PE, Bernado P, Fogerty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 2008; 46: 1142-1151.